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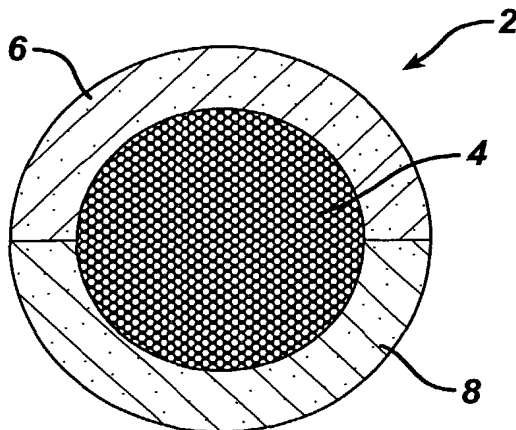
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(54) Title: MODIFIED RELEASE DOSAGE FORMS



(57) Abstract: A dosage form comprises: (a) at least one active ingredient; (b) a core; and (c) a shell which surrounds the core, wherein the shell is substantially free of pores having a diameter of 0.5-5.0 microns, and the shell comprises a first shell portion and a second shell portion which are compositionally different and the dosage form provides a modified release profile of the active ingredient upon contacting of the dosage form with a liquid medium. In another embodiment, the dosage form comprises: (a) at least one active ingredient; (b) a core comprising first and second core portions; and (c) a shell which surrounds the core, wherein the shell comprises first and second shell portions such that the first shell portion resides upon the first core portion and the second shell portion resides upon the second core portion, and at least one of the first or second shell portions or first or second shell portions provides a modified release profile of the active ingredient upon contacting of the dosage form with a liquid medium.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MODIFIED RELEASE DOSAGE FORMS

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] This invention relates to modified release dosage forms such as modified release pharmaceutical compositions. More particularly, this invention relates to modified release dosage forms having a two-portion shell for delivering one or more active ingredients in a controlled or delayed manner upon contacting of the dosage form with a liquid medium.

2. Background Information

[0002] Modified release pharmaceutical dosage forms have long been used to optimize drug delivery and enhance patient compliance, especially by reducing the number of doses of medicine the patient must take in a day. For this purpose, it is often desirable to modify the rate of release of a drug (one particularly preferred type of active ingredient) from a dosage form into the gastro-intestinal (g.i.) fluids of a patient, especially to slow the release to provide prolonged action of the drug in the body.

[0003] The rate at which an orally delivered pharmaceutical active ingredient reaches its site of action in the body depends on a number of factors, including the rate and extent of drug absorption through the g.i. mucosa. To be absorbed into the circulatory system (blood), the drug must first be dissolved in the g.i. fluids. For many drugs, diffusion across the g.i. membranes is relatively rapid compared to dissolution. In these cases, the dissolution of the active ingredient is the rate limiting step in drug absorption, and controlling the rate of dissolution allows the formulator to control the rate of drug absorption into the circulatory system of a patient.

[0004] An important objective of modified release dosage forms is to provide a desired blood concentration versus time (pharmacokinetic, or PK) profile for the drug. Fundamentally, the PK profile for a drug is governed by the rate of absorption of the drug into the blood, and the rate of elimination of the drug from the blood. The type of PK profile desired depends, among other factors, on the particular active ingredient, and physiological condition being treated.

[0005] A particularly desirable PK profile for a number of drugs and conditions is one in which the level of drug in the blood is maintained essentially constant (i.e. the rate of drug absorption is approximately equal to the rate of drug elimination) over a relatively long period of time. Such systems have the benefit of reducing the frequency of dosing, improving patient compliance, as well as minimizing side effects while maintaining full therapeutic efficacy. A dosage form which provides a "zero-order," or constant release rate of the drug is useful for this purpose. Since zero-order release systems are difficult to achieve, systems which approximate a constant release rate, such as for example first-order and square root of time profiles are often used to provide sustained (e.g. prolonged, extended, or retarded) release of a drug.

[0006] Another particularly desirable PK profile is achieved by a dosage form that delivers a delayed release dissolution profile, in which the release of drug from the dosage form is delayed for a pre-determined time after ingestion by the patient. The delay period ("lag time") can be followed either by prompt release of the active ingredient ("delayed burst"), or by sustained (prolonged, extended, or retarded) release of the active ingredient ("delayed then sustained").

[0007] Another particularly desirable PK profile, is a "pulsatile" profile, in which for example, a first dose is delivered immediately, followed by a delay corresponding

approximately to the time during which a therapeutic concentration of the first dose is maintained in the blood, followed by either prompt or sustained release of a subsequent dose of the same drug.

[0008] It is also particularly desirable for a pharmaceutical dosage form to deliver more than one drug at a modified rate. Because the onset and duration of the therapeutic efficacy of drugs vary widely, as do their absorption, distribution, metabolism, and elimination, it is often desirable to modify the release of different drugs in different ways, or to have a first active ingredient immediately released from the dosage form, while a second drug is released in a delayed, controlled, sustained, prolonged, extended, or retarded manner.

[0009] Well known mechanisms by which a dosage form (or drug delivery system) can deliver drug at a controlled rate (e.g. sustained, prolonged, extended or retarded release) include diffusion, erosion, and osmosis.

[0010] One classic diffusion-controlled release system comprises a "reservoir" containing the active ingredient, surrounded by a "membrane" through which the active ingredient must diffuse to be absorbed into the bloodstream of the patient. The rate of drug release, dM/dt depends on the area (A) of the membrane, the diffusional pathlength (l), the concentration gradient (ΔC) of the drug across the membrane, the partition coefficient (K) of the drug into the membrane, and the diffusion coefficient (D):

$$dM/dt = \{ADK\Delta C\} / l$$

[0011] Since one or more of the above terms, particularly the diffusional pathlength, and concentration gradient tend to be non-constant, diffusion-controlled systems generally deliver a non-constant release rate. In general, the rate of drug release from diffusion-controlled release systems typically follows first order kinetics.

[0012] Another common type of diffusion-controlled release system comprises active ingredient, distributed throughout an insoluble porous matrix through which the active ingredient must diffuse in order to be absorbed into the bloodstream of the patient. The amount of drug release (M) at a given time at sink conditions (i.e. drug concentration at the matrix surface is much greater than drug concentration in the bulk solution) depends on the area (A) of the matrix, the diffusion coefficient (D), the porosity (E) and tortuosity (T) of the matrix, the drug solubility (Cs) in the dissolution medium, time (t) and the drug concentration (Cp) in the dosage form:

$$M = A (DE/T(2C_p - EC_s) (C_s) t)^{1/2}$$

[0013] It will be noted in the above relationship that the amount of drug released is generally proportional to the square root of time. Assuming factors such as matrix porosity and tortuosity are constant within the dosage form, a plot of amount of drug released versus the square root of time should be linear.

[0014] A commonly used erosion-controlled release system comprises a "matrix" throughout which the drug is distributed. The matrix typically comprises a material which swells at the surface, and slowly dissolves away layer by layer, liberating drug as it dissolves. The rate of drug release (dM/dt) in these systems depends on the rate of erosion (dx/dt) of the matrix, the concentration profile in the matrix, and the surface area (A) of the system:

$$dM/dt = A \{dx/dt\} \{f(C)\}$$

[0015] Again, variation in one or more terms, such as surface area, typically lead to a non-constant release rate of drug. In general, the rate of drug release from erosion-controlled release systems typically follows first order kinetics.

[0016] Another type of erosion controlled delivery system employs materials which swell and dissolve slowly by surface erosion to provide a delayed release of pharmaceutical

active ingredient. Delayed release is useful, for example in pulsatile or repeat action delivery systems, in which an immediate release dose is delivered, followed by a pre-determined lag time before a subsequent dose is delivered from the system. In these systems, the lag time (T_1) depends on the thickness (h) of the erodible layer, and the rate of erosion (dx/dt) of the matrix, which in turn depends on the swelling rate and solubility of the matrix components:

$$T_1 = h \ (dx/dt)$$

[0017] The cumulative amount of drug (M) released from these systems at a given time generally follows the equation:

$$M = (dM/dt) (t - T_1)$$

where dM/dt is generally described by either the diffusion-controlled or erosion-controlled equations above, and T_1 is the lag time.

[0018] It is often practical to design dosage forms which use a combination of the above mechanisms to achieve a particularly desirable release profile for a particular active ingredient. It will be readily recognized by those skilled in the art that a dosage form construct which offers multiple compartments, such as for example multiple core portions and/or multiple shell portions, is particularly advantageous for its flexibility in providing a number of different mechanisms for controlling the release of one or more active ingredients.

[0019] Current core-shell systems are limited by the available methods for manufacturing them, as well as the materials that are suitable for use with the current methods. A shell, or coating, which confers modified release properties is typically applied via conventional methods, such as for example, spray-coating in a coating pan. Pan-coating produces a single shell which essentially surrounds the core. The single shell is inherently limited in its functionality. It is possible via pan-coating to apply multiple concentric shells, each with a different functionality, however such systems are limited in that the outer shell

must first dissolve before the functionality conferred by each successive layer can be realized. It is also known, via pan coating, to deliver a first dose of active ingredient from a coating, and a second dose of active ingredient from a core. Dosage forms having sprayed coatings which provide delayed release are described, for example, in G. Maffione et al., "High-Viscosity HPMC as a Film-Coating Agent," *Drug Development and Industrial Pharmacy* (1993) 19(16), pp. 2043-2053. U.S. Patent No. 4,576,604, for example, discloses an osmotic device (dosage form) comprising a drug compartment surrounded by a wall (coating) in which the coating may comprise an immediate release dose of drug, and the inner drug compartment may comprise a sustained release dose of drug. The coating compositions that can be applied via spraying are limited by their viscosity. High viscosity solutions are difficult or impractical to pump and deliver through a spray nozzle. Spray coating methods suffer the further limitations of being time-intensive and costly. Several hours of spraying may be required to spray an effective amount of coating to control the release of an active ingredient. Coating times of 8 to 24 hours are not uncommon.

[0020] Alternately, conventional modified release systems may be prepared by compression, to produce either multiple stacked layers, or core and shell configurations. Modified release dosage forms prepared via compression are exemplified in U.S. Patent Nos. 5,738,874 and 6,294,200, and WO 99/51209. It is possible, via compression-coating, to produce a 2-portion shell, which may function as a barrier, or release delaying coating, however compression-coated systems are limited by the shell thickness and shell composition. Günsel et al., "Compression-coated and layer tablets" in *Pharmaceutical Dosage Forms – Tablets*, edited by H. A. Lieberman, L. Lachman, J. B. Schwartz (2nd ed., rev. and expanded. Marcel Dekker, Inc.) pp. 247-284, for example discloses the thickness of compression coated shells is typically between 800 and 1200 microns. Because of these limitations, compression-coated dosage forms are not optimal for providing certain types of

modified release, such as for example diffusion-controlled release which is not preceded by a lag-time. U.S. Patent No. 5,738,874, discloses a 3-layer pharmaceutical compressed tablet capable of liberating one or more drugs at different release rates, in which an immediate release dose of active may be contained in a compressed coating layer, and the compressed coating layer has a weight which is 230% to 250% of the weight of the core, and a sustained release dose of active ingredient is contained in the core. Alternatively the outer compressed coating layer may function via an erosion mechanism to delay release of an active ingredient contained in the core. U.S. Patent No. 5,464,633, for example, discloses delayed-release dosage forms in which an external coating layer was applied by a compression coating process. The coating level ranged from 105 percent to 140 percent of the weight of the core in order to yield product with the desired time delayed profile.

[0021] It is one object of this invention to provide a dosage form in which at least one active ingredient contained therein exhibits a modified release profile upon contacting of the dosage form with a liquid medium. Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description set forth below.

SUMMARY OF THE INVENTION

[0022] In one embodiment, the dosage form of this invention comprises: (a) at least one active ingredient; (b) a core; and (c) a shell which resides upon at least a portion of the core, wherein the shell is substantially free of pores having a diameter of 0.5 to 5.0 microns, the shell comprises a first shell portion and a second shell portion which are compositionally different and the dosage form provides a modified release profile of the active ingredient upon contacting of the dosage form with a liquid medium.

[0023] In another embodiment, the dosage form of this invention comprises: (a) at least one active ingredient; (b) a core comprising first and second core portions; and (c) a shell portion which surrounds at least one of the first or second core portions.

[0024] In another embodiment, the dosage form of this invention comprises: (a) at least one active ingredient; (b) a core comprising first and second core portions; and (c) a shell portion which surrounds only the first core portion, wherein the second core portion is not enclosed by a shell portion, and is exposed immediately to the liquid medium upon contact of the dosage form with a liquid medium.

[0025] In another embodiment, the dosage form of this invention comprises: (a) at least one active ingredient; (b) a core comprising first and second core portions; and (c) a shell which resides upon at least a portion of the core, wherein the shell comprises first and second shell portions such that the first shell portion resides upon at least a portion of the first core portion and the second shell portion resides upon at least a portion of the second core portion, and at least one of the first or second core portions or first or second shell portions provides a modified release profile of an active ingredient upon contacting of the dosage form with a liquid medium.

[0026] In another embodiment, at least one of the first or second shell portions comprises an active ingredient.

[0027] In another embodiment, the first and second shell portions each comprise an active ingredient.

[0028] In another embodiment, at least one of the first or second shell portions comprises an active ingredient which is immediately released therefrom upon contacting of the dosage form with a liquid medium.

[0029] In another embodiment, at least one of the first or second shell portions provides modified release of at least one active ingredient contained therein.

[0030] In another embodiment, at least one of the first or second shell portions comprises at least one active ingredient, and the release of the active ingredient contained in the shell portion is sustained, prolonged, extended, or retarded upon contacting of the dosage form with a liquid medium.

[0031] In another embodiment, the first and second shell portions each provide different release profiles for the active ingredients contained therein upon contacting of the dosage form with a liquid medium.

[0032] In another embodiment, at least one of the first or second shell portions provides modified release of at least one active ingredient contained in the underlying core or portion thereof.

[0033] In another embodiment, the core comprises particles comprising at least one active ingredient.

[0034] In another embodiment, the particles comprise a coating capable of providing a modified release profile of the active ingredient in the particles upon contacting of the core with a liquid medium.

[0035] In another embodiment, the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and at least one active ingredient contained in the first or second core portion exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

[0036] In another embodiment, the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the materials comprising the first or second core portion provide a modification to the release of an active ingredient contained therein upon contacting of the dosage form with a liquid medium.

[0037] In another embodiment, the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the materials comprising the first or second shell portion provide a modification to the release of an active ingredient contained in the underlying core portion upon contacting of the dosage form with a liquid medium.

[0038] In another embodiment, the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the release of the active ingredient contained in the core portion is delayed upon contacting of the dosage form with a liquid medium.

[0039] In another embodiment, the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the release of the active ingredient contained in the core portion is sustained, prolonged, extended, or retarded upon contacting of the dosage form with a liquid medium.

[0040] In another embodiment, at least one of the first or second core portions comprises an active ingredient which is immediately released therefrom upon breach of the surrounding shell portion and contacting of the core portion with a liquid medium.

[0041] In another embodiment, the core comprises a first core portion and a second core portion, each core portion comprises an active ingredient, and each of the active

ingredients exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

[0042] In another embodiment, the release profiles of the active ingredients in the first and second core portions are substantially similar.

[0043] In another embodiment, the release profiles of the first and second core portions are substantially different.

[0044] In another embodiment, the core comprises a first core portion and a second core portion, only one of the first or second core portions comprises one or more active ingredients, and at least one active ingredient exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

[0045] In another embodiment, the core is a bi-layer tablet.

[0046] In another embodiment, at least one of the first or second core portions comprises particles comprising at least one active ingredient.

[0047] In another embodiment, the particles comprise a coating capable of providing a modified release profile of the active ingredient in the particles upon contacting of the core with a liquid medium.

[0048] In another embodiment, the core is substantially free of pores having a diameter of 0.5-5.0 microns.

[0049] In another embodiment, the first core portion comprises a first active ingredient, and the second core portion does not comprise an active ingredient.

[0050] In another embodiment, the first core portion comprises a first active ingredient, and the second core portion comprises a second active ingredient.

[0051] In another embodiment, the first shell portion provides for modified release of the first active ingredient, and the second shell portion provides for modified release of the second active ingredient.

[0052] In another embodiment, the first shell portion provides for immediate release of the first active ingredient, and the second shell portion provides for modified release of the second active ingredient.

[0053] In another embodiment, the first core portion comprises a first active ingredient, the second core portion comprises a second active ingredient, the first shell portion comprises a third active ingredient, and the second shell portion comprises a fourth active ingredient.

[0054] In another embodiment, at least one of the first or second core portions is substantially free of pores having a diameter of 0.5-5.0 microns.

[0055] In another embodiment, at least one of the first or second shell portions is substantially free of pores having a diameter of 0.5-5.0 microns.

[0056] In another embodiment, one or more shell portions functions as a barrier to prevent release therethrough of an active ingredient contained in the underlying core or core portion.

[0057] In another embodiment, at least one of the first or second shell portions comprises a thermal-reversible carrier selected from the group consisting of polyethylene glycol, polyethylene oxide and combinations thereof.

[0058] In another embodiment, at least one of the first or second shell portions comprises a release modifying excipient selected from the group consisting of shellac, hydroxypropylmethylcellulose, polyethylene oxide, ammonio methacrylate copolymer type B, and combinations thereof.

[0059] In another embodiment, at least one of the first or second shell portions comprises a film-former selected from the group consisting of cellulose acetate, ammonio methacrylate copolymer type B, shellac, hydroxypropylmethylcellulose, and combinations thereof.

[0060] In another embodiment, at least one of the first or second shell portions comprises a swellable erodible hydrophilic material selected from the group consisting of selected from cross-linked polyvinyl pyrrolidone, cross-linked agar, cross-linked carboxymethylcellulose sodium, and combinations thereof.

[0061] In another embodiment, at least one of the first or second shell portions further comprises a plasticizer.

[0062] In another embodiment, at least one of the first or second shell portions comprises a pore former.

[0063] In another embodiment, an outer coating covers at least a portion of the shell.

[0064] In another embodiment, the shell is prepared using a solvent-free molding process.

[0065] In another embodiment, the shell comprises at least 30% by weight of a thermal-reversible carrier.

[0066] In another embodiment, the shell comprises up to 55% by weight of a swellable, erodible hydrophilic material.

[0067] In another embodiment, the shell is prepared using a solvent-based molding process.

[0068] In another embodiment, the shell comprises at least 15% by weight of a film-former.

[0069] In another embodiment, the shell comprises at least 55% by weight of a release-modifying agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0070] Figs. 1 depicts a cross-sectional side view of one embodiment of the dosage form of this invention.

[0071] Fig. 2 depicts a cross-sectional side view of another embodiment of the dosage form of this invention.

[0072] Fig. 3 depicts the % release of active ingredient vs. time measured for the dosage form of Example 1.

[0073] Fig. 4 depicts the % release of active ingredient vs. time measured for the dosage form of Example 2.

DETAILED DESCRIPTION OF THE INVENTION

[0074] As used herein, the term "dosage form" applies to any solid object, semi-solid, or liquid composition designed to contain a specific pre-determined amount (dose) of a certain ingredient, for example an active ingredient as defined below. Suitable dosage forms may be pharmaceutical drug delivery systems, including those for oral administration, buccal

administration, rectal administration, topical or mucosal delivery, or subcutaneous implants, or other implanted drug delivery systems; or compositions for delivering minerals, vitamins and other nutraceuticals, oral care agents, flavorants, and the like. Preferably the dosage forms of the present invention are considered to be solid, however they may contain liquid or semi-solid components. In a particularly preferred embodiment, the dosage form is an orally administered system for delivering a pharmaceutical active ingredient to the gastro-intestinal tract of a human.

[0075] The dosage forms of the invention exhibit modified release of one or more active ingredients contained therein. The active ingredient or ingredients may be found within the core, the shell, or a portion or combination thereof. As used herein, the term "modified release" shall apply to dosage forms, coatings, shells, cores, portions thereof, or compositions that alter the release of an active ingredient in any manner. The active ingredient or ingredients that are released in a modified manner may be contained within the coating, shell, core, composition, or portion thereof providing the modification. Alternatively the modified release active ingredient may be contained in a different portion of the dosage form from the coating, shell, core, composition, or portion thereof providing the modification; for example the modified release active ingredient may be contained in a core portion, and the modification may be provided by the overlaying shell portion. Types of modified release include controlled, prolonged, sustained, extended, delayed, pulsatile, repeat action, and the like. Suitable mechanisms for achieving these types of modified release include diffusion, erosion, surface area control via geometry and/or impermeable barriers, or other mechanisms known in the art. Moreover, the modified release properties of the dosage form may be achieved through design of the core or a portion thereof, or the first shell portion, or the second shell portion, or a combination of two or more of these parts of the dosage form.

[0076] The dissolution profile of each active ingredient from the dosage form may be governed by a sum of contributions from the properties of the various portions. Additionally, a single portion, for example a core portion, may possess a combination of erosional and diffusional properties. In any case, the dissolution rate of a particular active ingredient from the dosage form will be the sum of the contributions from all the various mechanisms contributed by the various portions of the dosage form which effect the release of that particular active ingredient, as depicted by the following equation:

$$Rate_{total} \dots = \dots X_1 Rate_1 \dots + X_2 Rate_2 \dots + X_3 Rate_3 \dots + X_n Rate_n$$

where $X_1, X_2, X_3, \dots X_n$ are the relative contribution fractions of to the total release rate, and $Rate_1, Rate_2, Rate_3, \dots Rate_n$ are the various release rates contributed by effects of the various portions of the dosage form on a particular active ingredient.

[0077] Suitable active ingredients for use in this invention include for example pharmaceuticals, minerals, vitamins and other nutraceuticals, oral care agents, flavorants and mixtures thereof. Suitable pharmaceuticals include analgesics, anti-inflammatory agents, antiarthritics, anesthetics, antihistamines, antitussives, antibiotics, anti-infective agents, antivirals, anticoagulants, antidepressants, antidiabetic agents, antiemetics, antiflatulents, antifungals, antispasmodics, appetite suppressants, bronchodilators, cardiovascular agents, central nervous system agents, central nervous system stimulants, decongestants, oral contraceptives, diuretics, expectorants, gastrointestinal agents, migraine preparations, motion sickness products, mucolytics, muscle relaxants, osteoporosis preparations, polydimethylsiloxanes, respiratory agents, sleep-aids, urinary tract agents and mixtures thereof.

[0078] Suitable oral care agents include breath fresheners, tooth whiteners, antimicrobial agents, tooth mineralizers, tooth decay inhibitors, topical anesthetics, mucoprotectants, and the like.

[0079] Suitable flavorants include menthol, peppermint, mint flavors, fruit flavors, chocolate, vanilla, bubblegum flavors, coffee flavors, liqueur flavors and combinations and the like.

[0080] Examples of suitable gastrointestinal agents include antacids such as calcium carbonate, magnesium hydroxide, magnesium oxide, magnesium carbonate, aluminum hydroxide, sodium bicarbonate, dihydroxyaluminum sodium carbonate; stimulant laxatives, such as bisacodyl, cascara sagrada, danthron, senna, phenolphthalein, aloe, castor oil, ricinoleic acid, and dehydrocholic acid, and mixtures thereof; H₂ receptor antagonists, such as famotadine, ranitidine, cimetadine, nizatidine; proton pump inhibitors such as omeprazole or lansoprazole; gastrointestinal cytoprotectives, such as sucralfate and misoprostol; gastrointestinal prokinetics, such as prucalopride, antibiotics for H. pylori, such as clarithromycin, amoxicillin, tetracycline, and metronidazole; antidiarrheals, such as diphenoxylate and loperamide; glycopyrrolate; antiemetics, such as ondansetron, analgesics, such as mesalamine.

[0081] In one embodiment of the invention, the active ingredient may be selected from bisacodyl, famotadine, ranitidine, cimetidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, antacids, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0082] In another embodiment, the active ingredient is selected from analgesics, anti-inflammatories, and antipyretics, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), including propionic acid derivatives, e.g. ibuprofen, naproxen, ketoprofen and the like; acetic

acid derivatives, e.g. indomethacin, diclofenac, sulindac, tolmetin, and the like; fenamic acid derivatives, e.g. mefenamic acid, meclofenamic acid, flufenamic acid, and the like; biphenylcarboxylic acid derivatives, e.g. diflunisal, flufenisal, and the like; and oxicams, e.g. piroxicam, sudoxicam, isoxicam, meloxicam, and the like. In a particularly preferred embodiment, the active ingredient is selected from propionic acid derivative NSAID, e.g. ibuprofen, naproxen, flurbiprofen, fenbufen, fenoprofen, indoprofen, ketoprofen, fluprofen, piroprofen, carprofen, oxaprozin, pranoprofen, suprofen, and pharmaceutically acceptable salts, derivatives, and combinations thereof. In a particular embodiment of the invention, the active ingredient may be selected from acetaminophen, acetyl salicylic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, diclofenac, cyclobenzaprine, meloxicam, rofecoxib, celecoxib, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0083] In another embodiment of the invention, the active ingredient may be selected from pseudoephedrine, phenylpropanolamine, chlorpheniramine, dextromethorphan, diphenhydramine, astemizole, terfenadine, fexofenadine, loratadine, desloratadine, cetirizine, mixtures thereof and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

[0084] Examples of suitable polydimethylsiloxanes, which include, but are not limited to dimethicone and simethicone, are those disclosed in United States Patent Nos. 4,906,478, 5,275,822, and 6,103,260, the contents of each is expressly incorporated herein by reference. As used herein, the term "simethicone" refers to the broader class of polydimethylsiloxanes, including but not limited to simethicone and dimethicone.

[0085] The active ingredient or ingredients are present in the dosage form in a therapeutically effective amount, which is an amount that produces the desired therapeutic response upon oral administration and can be readily determined by one skilled in the art. In determining such amounts, the particular active ingredient being administered, the

bioavailability characteristics of the active ingredient, the dosing regimen, the age and weight of the patient, and other factors must be considered, as known in the art. Typically, the dosage form comprises at least about 1 weight percent, preferably, the dosage form comprises at least about 5 weight percent, e.g. about 20 weight percent of a combination of one or more active ingredients. In one preferred embodiment, the core comprises a total of at least about 25 weight percent (based on the weight of the core) of one or more active ingredients.

[0086] The active ingredient or ingredients may be present in the dosage form in any form. For example, the active ingredient may be dispersed at the molecular level, e.g. melted or dissolved, within the dosage form, or may be in the form of particles, which in turn may be coated or uncoated. If the active ingredient is in form of particles, the particles (whether coated or uncoated) typically have an average particle size of about 1-2000 microns. In one preferred embodiment, such particles are crystals having an average particle size of about 1-300 microns. In another preferred embodiment, the particles are granules or pellets having an average particle size of about 50-2000 microns, preferably about 50-1000 microns, most preferably about 100-800 microns.

[0087] In embodiments where an active ingredient is contained within the core, at least a portion of the active ingredient may be optionally coated with a release-modifying coating, as known in the art. This advantageously provides an additional tool for modifying the release profile of active ingredient from the dosage form. For example, the core may contain coated particles of one or more active ingredients, in which the particle coating confers a release modifying function, as is well known in the art. Examples of suitable release modifying coatings for particles are described in U.S. Patent Nos. 4,173,626; 4,863,742; 4,980,170; 4,984,240; 5,286,497; 5,912,013; 6,270,805; and 6,322,819. Commercially available modified release coated active particles may also be employed.

Accordingly, all or a portion of one or more active ingredients in the core may be coated with a release-modifying material.

[0088] In embodiments in which it is desired for the active ingredient to be absorbed into the systemic circulation of an animal, the active ingredient or ingredients are preferably capable of dissolution upon contact with a fluid such as water, gastric fluid, intestinal fluid or the like. In one embodiment, the dissolution characteristics of at least one active ingredient meets USP specifications for immediate release tablets containing the active ingredient. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19 – 20 and 856 (1999). In embodiments in which at least one active ingredient is released immediately, the immediately released active ingredient is preferably contained in the shell or on the surface of the shell, e.g. in a further coating surrounding at least a portion of the shell. In another embodiment, the dissolution characteristics of one or more active ingredients are modified: e.g. controlled, sustained, extended, retarded, prolonged, delayed and the like. In a preferred embodiment in which one or more active ingredients are released in a modified manner, the modified release active or actives are preferably contained in the core.

[0089] A first embodiment of this invention is depicted in Fig. 1, which is a cross-sectional side view of a dosage form 2 which comprises a core 4 and first and second shell portions 6 and 8, respectively, which in this embodiment surround the core. In other

embodiments of this invention, the first and second shell portions 6 and 8 may reside upon a portion of the core 4 without surrounding the core 4.

[0090] A second embodiment of this invention is depicted in Fig. 2, which is a cross-sectional side view of a dosage form 202 which comprises a core 204 having first and second portions 203 and 205, respectively, and first and second shell portions 206 and 208, respectively, which in this embodiment surround the core. In other embodiments of this invention, the first and second shell portions 206 and 208 may reside upon first and second core portions 203 and 205, respectively, without surrounding the core 204.

[0091] In certain embodiments of the invention, one or more shell portions contain active ingredient which is released essentially immediately upon ingestion of the dosage form. In these embodiments, the shell portion preferably comprises materials which exhibit rapid dissolution in gastro-intestinal fluids.

[0092] In certain other embodiments, one or more shell portions function as a diffusional membrane which contains pores through which fluids can enter the dosage form, and dissolved active ingredient can be released in a sustained, extended, prolonged or retarded manner. In these embodiments, the rate of release of active ingredient from an underlying core portion will depend upon the total pore area in the shell portion, the pathlength of the pores, and the solubility and diffusivity of the active ingredient (in addition to its rate of release from the core portion itself). In preferred embodiments in which a shell portion functions as a diffusional membrane, the release of the active ingredient from the dosage form may be described as controlled, prolonged, sustained or extended. In these embodiments, the contribution to active ingredient dissolution from the subject shell portion may follow zero-order, first-order, or square-root of time kinetics. In certain such embodiments, the diffusional membrane shell portion preferably comprises a release-

modifying excipient such as a combination of a pore former and an insoluble edible material such as for example a film forming water insoluble polymer. Alternately, in such embodiments in which the shell portion is prepared by solven-free molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[0093] In certain other embodiments, one or more shell portions function as an eroding matrix from which active ingredient dispersed in the shell portion is liberated by the dissolution of successive layers of the shell portion surface. In these embodiments, the rate of active ingredient release will depend on the dissolution rate of the matrix material in the shell portion. Particularly useful matrix materials for providing surface erosion include those which first absorb liquid, then swell and/or gel prior to dissolving. In certain such embodiments, the eroding matrix shell portion preferably comprises a swellable erodible hydrophilic material.

[0094] In certain other embodiments, one or more shell portions function as a barrier to prevent release therethrough of an active ingredient contained in the underlying core or core portion. In such embodiments, active ingredient is typically released from a portion of the core which is not covered by the barrier shell portion. Such embodiments advantageously allow for control of the surface area for release of the active ingredient. In certain particular embodiments, for example, the surface area for release of active ingredient can be maintained substantially constant over time. In a particularly preferred embodiment, the release of at least one active ingredient follows substantially zero-order kinetics. In certain such embodiments, the barrier shell portion preferably comprises a water insoluble material such as for example a water insoluble polymer.

[0095] In certain other embodiments, one or more shell portions function as a delayed release coating to delay release of an active ingredient which is contained in the core or a portion thereof. In these embodiments, the lag-time for onset of active ingredient release may be governed by erosion of the coating or diffusion through the coating or a combination thereof. In certain such embodiments, the eroding matrix shell portion preferably comprises a swellable erodible hydrophilic material.

[0096] In embodiments in which one or more shell portions function to modify the release of an active ingredient which is contained in the core or the subject shell portion, the thickness of the shell portion is critical to the release properties of the dosage form. Advantageously the dosage forms of the invention can be made with precise control over shell thickness. In a preferred embodiment in which one or more shell portions function to modify the release of an active ingredient which is contained in the core or the subject shell portion, the shell portion or portions are made by the thermal cycle or thermal setting injection molding methods and apparatus described below.

[0097] In certain embodiments of the invention, one or more core portions function to promptly, e.g. immediately, release one or more active ingredients contained therein upon breach of the surrounding shell portion. In these embodiments, the core portion preferably comprises materials which exhibit rapid dissolution in gastro-intestinal fluids, for example the core portion may comprise a disintegrant.

[0098] In certain other embodiments, one or more core portions function as an eroding matrix from which dispersed active ingredient is liberated by the dissolution of successive layers of the matrix surface. In these embodiments, the rate of active ingredient release from the core portion will depend on the dissolution rate of the matrix material. Particularly useful eroding matrix materials for providing surface erosion include those which

first absorb liquid, then swell and/or gel prior to dissolving. In certain such embodiments, the eroding matrix core portion preferably comprises a swellable erodible hydrophilic material.

[0099] In certain other embodiments, one or more core portions function as a diffusional matrix. In these embodiments, the core portion preferably comprises active ingredient, distributed throughout an insoluble porous matrix, which contains pores or channels through which fluids can enter the core portion, and the active ingredient must diffuse to be released from the dosage form. In these embodiments, the rate of active ingredient release from the core portion will depend upon the area (A) of the matrix, the diffusion coefficient (D), the porosity (E) and tortuosity (T) of the matrix, the drug solubility (Cs) in the dissolution medium, and the drug concentration (Cp) in the dosage form. In preferred embodiments in which a core portion functions as a diffusional matrix, the release of the active ingredient from the core portion may be described as controlled, prolonged, sustained, or extended. In these embodiments, the contribution to active ingredient dissolution from the subject core portion may follow zero-order, first-order, or preferably square-root of time kinetics. In certain such embodiments, the diffusional matrix core portion preferably comprises a pore former.

[00100] In embodiments in which a core portion functions to modify release of an active ingredient contained therein, the release of active ingredient may be further modified by the function of a surrounding shell portion, as described above. In such embodiments, the release of the active ingredient from the dosage form will be governed by the sum of all the contributions acting upon it, e.g. from the relevant core and shell portions, and may be described as controlled, prolonged, sustained, extended, delayed, or pulsatile. In these embodiments, the dissolution of active ingredient from the dosage form may follow zero-order, first-order, or square-root of time kinetics.

[00101] In embodiments in which the core comprises multiple portions, the portions may comprise different materials, or be prepared by different methods, or both. In one particular embodiment a first core portion may be prepared by compression, and a second core portion may be prepared by molding.

[00102] In certain preferred embodiments, the core comprises multiple portions, which comprise different active ingredients or have different release-modifying properties, or both; and the shell comprises a corresponding number of multiple portions, which each cover a specific core portion in order to modify or further modify the release of one or more active ingredients contained within the respective core portion. For such embodiments, it is critical to have a manufacturing process which is capable of maintaining the orientation of the core prior to and during the application of each shell portion thereon. Advantageously, the orientation of the components of the dosage forms of the present invention can be precisely controlled, when manufactured using the thermal cycle and thermal setting apparatus and described below. In one such particularly preferred embodiment, the dosage form comprises a core comprising a first core portion and a second core portion which are compositionally different, wherein at least one of the first or second core portions comprises an active ingredient; and a shell which surrounds the core and comprises a first shell portion and a second shell portion which are compositionally different, wherein at least one of the first or second shell portions confers a modification to the release of an active ingredient contained in the underlying core portion.

[00103] In certain other embodiments of the invention, a further degree of flexibility in designing the dosage forms of the present invention can be achieved through the use of an additional outer coating overlaying the shell or one or more portions thereof. The additional outer coating may be applied for example by compression, or by molding. In such

embodiments, the dosage form of the invention comprises at least one active ingredient; a core; a shell which resides upon at least a portion of the core and comprises a first and second shell portion which are compositionally different; and an outer coating which covers at least a portion of the shell. The outer coating may for example cover a portion of the first shell portion, or the second shell portion, or both, or may surround the entire shell. In one particularly preferred embodiment, the outer coating comprises an active ingredient, which is released immediately (i.e. the dissolution of the active ingredient from the outer coating conforms to USP specifications for immediate release dosage forms of the particular active ingredient employed). In one such particularly preferred embodiment, the dosage form is a pulsatile drug delivery system, in which one or more shell portions provides for delayed release of a second dose of active ingredient, which is contained in an underlying core portion.

[00104] The core of the present invention may be prepared by any suitable method, including for example compression and molding, and depending on the method by which it is made, typically comprises active ingredient and a variety of excipients (inactive ingredients which may be useful for conferring desired physical properties to the dosage core).

[00105] In embodiments in which the core, or a portion thereof, is made by compression, suitable excipients include fillers, binders, disintegrants, lubricants, glidants, and the like, as known in the art. In embodiments in which the core is made by compression and additionally confers modified release of an active ingredient contained therein, the core preferably further comprises a release-modifying compressible excipient.

[00106] Suitable fillers for use in making the core, or a portion thereof, by compression include water-soluble compressible carbohydrates such as sugars, which include dextrose, sucrose, maltose, and lactose, sugar-alcohols, which include mannitol, sorbitol,

maltitol, xylitol, starch hydrolysates, which include dextrans, and maltodextrins, and the like, water insoluble plastically deforming materials such as microcrystalline cellulose or other cellulosic derivatives, water-insoluble brittle fracture materials such as dicalcium phosphate, tricalcium phosphate and the like and mixtures thereof.

[00107] Suitable binders for making the core, or a portion thereof, by compression include dry binders such as polyvinyl pyrrolidone, hydroxypropylmethylcellulose, and the like; wet binders such as water-soluble polymers, including hydrocolloids such as acacia, alginates, agar, guar gum, locust bean, carrageenan, carboxymethylcellulose, tara, gum arabic, tragacanth, pectin, xanthan, gellan, gelatin, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, inulin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan, polyvinyl pyrrolidone, cellulotics, sucrose, starches, and the like; and derivatives and mixtures thereof.

[00108] Suitable disintegrants for making the core, or a portion thereof, by compression, include sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and the like.

[00109] Suitable lubricants for making the core, or a portion thereof, by compression include long chain fatty acids and their salts, such as magnesium stearate and stearic acid, talc, glycerides and waxes.

[00110] Suitable glidants for making the core, or a portion thereof, by compression, include colloidal silicon dioxide, and the like.

[00111] Suitable release-modifying compressible excipients for making the core, or a portion thereof, by compression include swellable erodible hydrophillic materials, insoluble edible materials, pH-dependent polymers, and the like.

[00112] Suitable swellable erodible hydrophilic materials for use as release-modifying excipients for making the core, or a portion thereof, by compression include: water swellable cellulose derivatives, polyalkalene glycols, thermoplastic polyalkalene oxides, acrylic polymers, hydrocolloids, clays, gelling starches, and swelling cross-linked polymers, and derivatives, copolymers, and combinations thereof. Examples of suitable water swellable cellulose derivatives include sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxyphenylcellulose, hydroxyethylcellulose (HEC), hydroxypentylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose. Examples of suitable polyalkalene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkalene oxides include poly (ethylene oxide). Examples of suitable acrylic polymers include potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, CARBOPOL (high-molecular weight cross-linked acrylic acid homopolymers and copolymers), and the like. Examples of suitable hydrocolloids include alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, gelatin, whey, chitosan, zooglan, methylcellulose, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples of suitable gelling starches include acid hydrolyzed starches, swelling starches such as sodium starch glycolate, and derivatives thereof. Examples of suitable swelling cross-linked polymers include cross-linked polyvinyl pyrrolidone, cross-linked agar, and cross-linked carboxymethylcellulose sodium.

[00113] Suitable insoluble edible materials for use as release-modifying excipients for making the core, or a portion thereof, by compression include water-insoluble polymers, and low-melting hydrophobic materials. Examples of suitable water-insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof. Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurate, glyceryl myristate, GlycoWax-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, and phosphatidic acid. Examples of suitable waxes include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[00114] Suitable pH-dependent polymers for use as release-modifying excipients for making the core, or a portion thereof, by compression include enteric cellulose derivatives, for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename

EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[00115] Suitable pharmaceutically acceptable adjuvants for making the core, or a portion thereof, by compression include, preservatives; high intensity sweeteners such as aspartame, acesulfame potassium, sucralose, and saccharin; flavorants; colorants; antioxidants; surfactants; wetting agents; and the like and mixtures thereof.

[00116] In one embodiment, the core is prepared by the compression methods and apparatus described in copending U.S. patent application Serial No. 09/966,509, pages 16-27, the disclosure of which is incorporated herein by reference. Specifically, the core is made using a rotary compression module comprising a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus having a double row die construction as shown in Figure 6 of U.S. patent application Serial No. 09/966,509. The dies of the compression module are preferably filled using the assistance of a vacuum, with filters located in or near each die. The purge zone of the compression module includes an optional powder recovery system to recover excess powder from the filters and return the powder to the dies.

[00117] In certain preferred embodiments of the invention, the core, or the shell, or a portion thereof, is prepared by molding. In such embodiments, the core, or the shell, or a portion thereof, is made from a flowable material. The flowable material may be any edible material that is flowable at a temperature between about 37°C and 250°C, and that is solid, semi-solid, or can form a gel at a temperature between about -10°C and about 35°C. When it is in the fluid or flowable state, the flowable material may comprise a dissolved or molten

component, and optionally a solvent such as for example water or organic solvents, or combinations thereof. The solvent may be partially or substantially removed by drying.

[00118] Suitable flowable materials for making the core, or the shell, or a portion thereof by molding include those comprising thermoplastic materials; film formers; thickeners such as gelling polymers or hydrocolloids; low melting hydrophobic materials such as fats and waxes; non-crystallizable carbohydrates; and the like. Suitable molten components of the flowable material include thermoplastic materials, low melting hydrophobic materials, and the like. Suitable dissolved components for the flowable material include film formers, thickeners such as gelling polymers or hydrocolloids, non-crystallizable carbohydrates, and the like.

[00119] Suitable thermoplastic materials can be molded and shaped when heated, and include both water soluble and water insoluble polymers that are generally linear, not crosslinked, nor strongly hydrogen bonded to adjacent polymer chains. Examples of suitable thermoplastic materials include: thermoplastic water swellable cellulose derivatives, thermoplastic water insoluble cellulose derivatives, thermoplastic vinyl polymers, thermoplastic starches, thermoplastic polyalkylene glycols, thermoplastic polyalkylene oxides, and amorphous sugar-glass, and the like, and derivatives, copolymers, and combinations thereof. Examples of suitable thermoplastic water swellable cellulose derivatives include hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC). Examples of suitable thermoplastic water insoluble cellulose derivatives include cellulose acetate (CA), ethyl cellulose (EC), cellulose acetate butyrate (CAB), cellulose propionate. Examples of suitable thermoplastic vinyl polymers include polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP). Examples of suitable thermoplastic starches are disclosed for example in U.S. Patent No. 5,427,614. Examples of suitable thermoplastic

polyalkalene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkalene oxides include polyethylene oxide having a molecular weight from about 100,000 to about 900,000 Daltons. Other suitable thermoplastic materials include sugar in the form on an amorphous glass such as that used to make hard candy forms.

[00120] Any film former known in the art is suitable for use in the flowable material of the present invention. Examples of suitable film formers include, but are not limited to, film-forming water soluble polymers, film-forming proteins, film-forming water insoluble polymers, and film-forming pH-dependent polymers. In one embodiment, the film-former for making the core or shell or portion thereof by molding may be selected from cellulose acetate, ammonio methacrylate copolymer type B, shellac, hydroxypropylmethylcellulose, and polyethylene oxide, and combinations thereof.

[00121] Suitable film-forming water soluble polymers include water soluble vinyl polymers such as polyvinylalcohol (PVA); water soluble polycarbohydrates such as hydroxypropyl starch, hydroxyethyl starch, pullulan, methylethyl starch, carboxymethyl starch, pre-gelatinized starches, and film-forming modified starches; water swellable cellulose derivatives such as hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), hydroxyethylmethylcellulose (HEMC), hydroxybutylmethylcellulose (HBMC), hydroxyethylethylcellulose (HEEC), and hydroxyethylhydroxypropylmethyl cellulose (HEMPMC); water soluble copolymers such as methacrylic acid and methacrylate ester copolymers, polyvinyl alcohol and polyethylene glycol copolymers, polyethylene oxide and polyvinylpyrrolidone copolymers; and derivatives and combinations thereof.

[00122] Suitable film-forming proteins may be natural or chemically modified, and include gelatin, whey protein, myofibrillar proteins, coagulatable proteins such as albumin,

casein, caseinates and casein isolates, soy protein and soy protein isolates, zein;; and polymers, derivatives and mixtures thereof.

[00123] Suitable film-forming water insoluble polymers, include for example ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof.

[00124] Suitable film-forming pH-dependent polymers include enteric cellulose derivatives, such as for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins, such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename, EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename, EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[00125] One suitable hydroxypropylmethylcellulose compound for use as a thermoplastic film-forming water soluble polymer is "HPMC 2910", which is a cellulose ether having a degree of substitution of about 1.9 and a hydroxypropyl molar substitution of 0.23, and containing, based upon the total weight of the compound, from about 29% to about 30% methoxyl groups and from about 7% to about 12% hydroxylpropyl groups. HPMC 2910 is commercially available from the Dow Chemical Company under the tradename METHOCEL E. METHOCEL E5, which is one grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 4 to 6 cps (4 to 6 millipascal-seconds) at 20°C in a

2% aqueous solution as determined by a Ubbelohde viscometer. Similarly, METHOCEL E6, which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 5 to 7 cps (5 to 7 millipascal-seconds) at 20°C in a 2% aqueous solution as determined by a Ubbelohde viscometer. METHOCEL E15, which is another grade of HPMC-2910 suitable for use in the present invention, has a viscosity of about 15000 cps (15 millipascal-seconds) at 20°C in a 2% aqueous solution as determined by a Ubbelohde viscometer. As used herein, "degree of substitution" shall mean the average number of substituent groups attached to a anhydroglucose ring, and "hydroxypropyl molar substitution" shall mean the number of moles of hydroxypropyl per mole anhydroglucose.

[00126] One suitable polyvinyl alcohol and polyethylene glycol copolymer is commercially available from BASF Corporation under the tradename KOLLICOAT IR.

[00127] As used herein, "modified starches" include starches that have been modified by crosslinking, chemically modified for improved stability or optimized performance, or physically modified for improved solubility properties or optimized performance. Examples of chemically-modified starches are well known in the art and typically include those starches that have been chemically treated to cause replacement of some of its hydroxyl groups with either ester or ether groups. Crosslinking, as used herein, may occur in modified starches when two hydroxyl groups on neighboring starch molecules are chemically linked. As used herein, "pre-gelatinized starches" or "instantized starches" refers to modified starches that have been pre-wetted, then dried to enhance their cold-water solubility. Suitable modified starches are commercially available from several suppliers such as, for example, A.E. Staley Manufacturing Company, and National Starch & Chemical Company. One suitable film forming modified starch includes the pre-gelatinized waxy maize derivative starches that are commercially available from National Starch & Chemical Company under the tradenames

PURITY GUM and FILMSET, and derivatives, copolymers, and mixtures thereof. Such waxy maize starches typically contain, based upon the total weight of the starch, from about 0 percent to about 18 percent of amylose and from about 100% to about 88% of amylopectin.

[00128] Another suitable film forming modified starch includes the hydroxypropylated starches, in which some of the hydroxyl groups of the starch have been etherified with hydroxypropyl groups, usually via treatment with propylene oxide. One example of a suitable hydroxypropyl starch that possesses film-forming properties is available from Grain Processing Company under the tradename, PURE-COTE B790.

[00129] Suitable tapioca dextrins for use as film formers include those available from National Starch & Chemical Company under the tradenames CRYSTAL GUM or K-4484, and derivatives thereof such as modified food starch derived from tapioca, which is available from National Starch and Chemical under the tradename PURITY GUM 40, and copolymers and mixtures thereof.

[00130] Any thickener known in the art is suitable for use in the flowable material of the present invention. Examples of such thickeners include but are not limited to hydrocolloids (also referred to herein as gelling polymers), clays, gelling starches, and crystallizable carbohydrates, and derivatives, copolymers and mixtures thereof.

[00131] Examples of suitable hydrocolloids (also referred to herein as gelling polymers) such as alginates, agar, guar gum, locust bean, carrageenan, tara, gum arabic, tragacanth, pectin, xanthan, gellan, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, gum arabic, inulin, pectin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples of suitable gelling starches include acid

hydrolyzed starches, and derivatives and mixtures thereof. Additional suitable thickening hydrocolloids include low-moisture polymer solutions such as mixtures of gelatin and other hydrocolloids at water contents up to about 30%, such as for example those used to make "gummi" confection forms.

[00132] Additional suitable thickeners include crystallizable carbohydrates, and the like, and derivatives and combinations thereof. Suitable crystallizable carbohydrates include the monosaccharides and the oligosaccharides. Of the monosaccharides, the aldohexoses e.g., the D and L isomers of allose, altrose, glucose, mannose, gulose, idose, galactose, talose, and the ketohexoses e.g., the D and L isomers of fructose and sorbose along with their hydrogenated analogs: e.g., glucitol (sorbitol), and mannitol are preferred. Of the oligosaccharides, the 1,2-disaccharides sucrose and trehalose, the 1,4-disaccharides maltose, lactose, and cellobiose, and the 1,6-disaccharides gentiobiose and melibiose, as well as the trisaccharide raffinose are preferred along with the isomerized form of sucrose known as isomaltulose and its hydrogenated analog isomalt. Other hydrogenated forms of reducing disaccharides (such as maltose and lactose), for example, maltitol and lactitol are also preferred. Additionally, the hydrogenated forms of the aldopentoses: e.g., D and L ribose, arabinose, xylose, and lyxose and the hydrogenated forms of the aldotetroses: e.g., D and L erythrose and threose are preferred and are exemplified by xylitol and erythritol, respectively.

[00133] In one embodiment of the invention, the flowable material comprises gelatin as a gelling polymer. Gelatin is a natural, thermogelling polymer. It is a tasteless and colorless mixture of derived proteins of the albuminous class which is ordinarily soluble in warm water. Two types of gelatin – Type A and Type B – are commonly used. Type A gelatin is a derivative of acid-treated raw materials. Type B gelatin is a derivative of alkali-treated raw materials. The moisture content of gelatin, as well as its Bloom strength,

composition and original gelatin processing conditions, determine its transition temperature between liquid and solid. Bloom is a standard measure of the strength of a gelatin gel, and is roughly correlated with molecular weight. Bloom is defined as the weight in grams required to move a half-inch diameter plastic plunger 4 mm into a 6.67% gelatin gel that has been held at 10°C for 17 hours. In a preferred embodiment, the flowable material is an aqueous solution comprising 20% 275 Bloom pork skin gelatin, 20% 250 Bloom Bone Gelatin, and approximately 60% water.

[00134] Suitable xanthan gums include those available from C.P. Kelco Company under the tradenames KELTROL 1000, XANTROL 180, or K9B310.

[00135] Suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof.

[00136] "Acid-hydrolyzed starch," as used herein, is one type of modified starch that results from treating a starch suspension with dilute acid at a temperature below the gelatinization point of the starch. During the acid hydrolysis, the granular form of the starch is maintained in the starch suspension, and the hydrolysis reaction is ended by neutralization, filtration and drying once the desired degree of hydrolysis is reached. As a result, the average molecular size of the starch polymers is reduced. Acid-hydrolyzed starches (also known as "thin boiling starches") tend to have a much lower hot viscosity than the same native starch as well as a strong tendency to gel when cooled.

[00137] "Gelling starches," as used herein, include those starches that, when combined with water and heated to a temperature sufficient to form a solution, thereafter form a gel upon cooling to a temperature below the gelation point of the starch. Examples of gelling starches include, but are not limited to, acid hydrolyzed starches such as that available from

Grain Processing Corporation under the tradename PURE-SET B950; hydroxypropyl distarch phosphate such as that available from Grain Processing Corporation under the tradename, PURE-GEL B990, and mixtures thereof.

[00138] Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurylate, glyceryl myristate, GlycoWax-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphotidyl choline, phosphotidyl serene, phosphotidyl enositol, and phosphotidic acid. Examples of suitable waxes include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[00139] Suitable non-crystallizable carbohydrates include non-crystallizable sugars such as polydextrose, and starch hydrolysates, e.g. glucose syrup, corn syrup, and high fructose corn syrup; and non-crystallizable sugar-alcohols such as maltitol syrup.

[00140] Suitable solvents for optional use as components of the flowable material for making the core, or the shell, or a portion thereof by molding include water; polar organic solvents such as methanol, ethanol, isopropanol, acetone, and the like; and non-polar organic solvents such as methylene chloride, and the like; and mixtures thereof.

[00141] The flowable material for making the core or the shell or a portion thereof by molding may optionally comprise adjuvants or excipients, which may comprise up to about

30% by weight of the flowable material. Examples of suitable adjuvants or excipients include plasticizers, detackifiers, humectants, surfactants, anti-foaming agents, colorants, flavorants, sweeteners, opacifiers, and the like. Suitable plasticizers for making the core, the shell, or a portion thereof, by molding include, but not be limited to polyethylene glycol; propylene glycol; glycerin; sorbitol; triethyl citrate; tributyl citrate; dibutyl sebecate; vegetable oils such as castor oil, rape oil, olive oil, and sesame oil; surfactants such as polysorbates, sodium lauryl sulfates, and dioctyl-sodium sulfosuccinates; mono acetate of glycerol; diacetate of glycerol; triacetate of glycerol; natural gums; triacetin; acetyltributyl citrate; diethyloxalate; diethylmalate; diethyl fumarate; diethylmalonate; dioctylphthalate; dibutylsuccinate; glyceroltributyrate; hydrogenated castor oil; fatty acids; substituted triglycerides and glycerides; and the like and/or mixtures thereof. In one embodiment, the plasticizer is triethyl citrate. In certain embodiments, the shell is substantially free of plasticizers, i.e. contains less than about 1%, say less than about 0.01% of plasticizers.

[00142] In one preferred embodiment, the flowable material comprises less than 5% humectants, or alternately is substantially free of humectants, such as glycerin, sorbitol, maltitol, xylitol, or propylene glycol. Humectants have traditionally been included in pre-formed films employed in enrobing processes, such as that disclosed in U.S. Patent Nos. 5,146,730 and 5,459,983, assigned to Banner Gelatin Products Corp., in order to ensure adequate flexibility or plasticity and bondability of the film during processing. Humectants function by binding water and retaining it in the film. Pre-formed films used in enrobing processes can typically comprise up to 45% water. Disadvantageously, the presence of humectant prolongs the drying process, and can adversely affect the stability of the finished dosage form.

[00143] In certain embodiments, the core, the shell, or portions thereof may be molded using a solvent-free process. In such embodiments, the core may comprise active ingredient contained within an excipient matrix. The matrix, or the core, or the shell, or portions thereof typically comprises at least about 30 percent, e.g. at least about 45 weight percent of a thermal-reversible carrier, and optionally up to about 30 weight percent of various adjuvants such as for example plasticizers, gelling agents, strengthening agents, colorants, stabilizers, preservatives, and the like as known in the art. The matrix or the core, or the shell, or portions thereof may optionally further comprise up to about 55 weight percent of one or more release-modifying moldable excipients as described below.

[00144] The core may be in a variety of different shapes. For example, the core may be shaped as a polyhedron, such as a cube, pyramid, prism, or the like; or may have the geometry of a space figure with some non-flat faces, such as a cone, truncated cone, cylinder, sphere, torus, or the like. In certain embodiments, the core has one or more major faces. For example in embodiments wherein the core is a compressed tablet, the core surface typically has two opposing major faces formed by contact with the upper and lower punch faces in the compression machine. In such embodiments the core surface typically further comprises a "belly-band" located between the two major faces, and formed by contact with the die walls in the compression machine. Exemplary core shapes which may be employed include tablet shapes formed from compression tooling shapes described by "The Elizabeth Companies Tablet Design Training Manual" (Elizabeth Carbide Die Co., Inc., p. 7 (McKeesport, Pa.) (incorporated herein by reference) as follows (the tablet shape corresponds inversely to the shape of the compression tooling):

1. Shallow Concave.
2. Standard Concave.
3. Deep Concave.
4. Extra Deep Concave.

5. Modified Ball Concave.
6. Standard Concave Bisect.
7. Standard Concave Double Bisect.
8. Standard Concave European Bisect.
9. Standard Concave Partial Bisect.
10. Double Radius.
11. Bevel & Concave.
12. Flat Plain.
13. Flat-Faced-Beveled Edge (F.F.B.E.).
14. F.F.B.E. Bisect.
15. F.F.B.E. Double Bisect.
16. Ring.
17. Dimple.
18. Ellipse.
19. Oval.
20. Capsule.
21. Rectangle.
22. Square.
23. Triangle.
24. Hexagon.
25. Pentagon.
26. Octagon.
27. Diamond.
28. Arrowhead.
29. Bullet.
30. Shallow Concave.
31. Standard Concave.
32. Deep Concave.
33. Extra Deep Concave.
34. Modified Ball Concave.
35. Standard Concave Bisect.
36. Standard Concave Double Bisect.
37. Standard Concave European Bisect.
38. Standard Concave Partial Bisect.
39. Double Radius.
40. Bevel & Concave.
41. Flat Plain.
42. Flat-Faced-Beveled Edge (F.F.B.E.).
43. F.F.B.E. Bisect.
44. F.F.B.E. Double Bisect.
45. Ring.
46. Dimple.
47. Ellipse.
48. Oval.
49. Capsule.
50. Rectangle.
51. Square.
52. Triangle.
53. Hexagon.
54. Pentagon.

55. Octagon.
56. Diamond.
57. Arrowhead.
58. Bullet.
59. Barrel.
60. Half Moon.
61. Shield.
62. Heart.
63. Almond.
64. House/Home Plate.
65. Parallelogram.
66. Trapezoid.
67. Figure 8/Bar Bell.
68. Bow Tie.
69. Uneven Triangle.

[00145] In one embodiment of the invention, the core comprises multiple portions, for example a first portion and a second portion. The portions may be prepared by the same or different methods and mated using various techniques, such as the thermal cycle molding and thermal setting molding methods described herein.. For example, the first and second portions may both be made by compression, or both may be made by molding. Or one portion may be made by compression and the other by molding. The same or different active ingredient may be present in the first and second portions of the core. Alternately, one or more core portions may be substantially free of active ingredients.

[00146] In certain embodiments of the invention, the core or a portion thereof may function to confer modified release properties to at least one active ingredient contained therein. In such embodiments, wherein the core or core portion is made by compression, as previously noted, the core preferably comprises a release-modifying compressible excipient. In such embodiments, wherein the core or core portion is made by molding, as previously noted, the core preferably comprises a release-modifying moldable excipient. In embodiments in which one or more core portions function as an eroding matrix from which dispersed active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying compressible or moldable

excipient selected from swellable erodible hydrophilic agents, pH-dependent polymers, and combinations thereof.

[00147] In embodiments in which one or more core portions function as a diffusional matrix through which active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore formers. Alternately, in such embodiments in which the core portion is prepared by molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[00148] The shell of the present invention comprises a first shell portion and a second shell portion that are compositionally different. For example the first and second shell portions may comprise different ingredients, or the first and second shell portions may comprise different levels of the same ingredients, e.g. colorants, opacifiers, film-formers, etc. In one such embodiment, the first and second shell portions may be visually distinct from one another, for example the visually distinct portions may be of different colors, hues, glosses, reflective qualities, brightness, depth, shades, chroma, opacity, etc. For example, the shell may have a red portion and a yellow portion, or a flat finish portion and a glossy portion, or an opaque portion and a translucent portion. Alternatively, the first and second shell portions may have different thickness. The first and second shell portions may have different functionalities. For example, the first and second shell portions may confer different release properties to an active ingredient contained in either the subject shell portion, or in a corresponding underlying core portion. In one particular embodiment, the first shell portion may function as a diffusional membrane which contains pores through which fluids can enter the dosage form, and dissolved active ingredient can be released from an underlying core

portion; and the second shell portion, may function as an eroding matrix from which active ingredient dispersed in the second shell portion is liberated by the dissolution of successive layers of the shell portion surface.

[00149] The shell portions of the present invention may be prepared by molding, using a solvent-free process, or a solvent-based process, and depending on the method used, typically comprise a variety of excipients which are useful for conferring desired properties to the shell portions. The shell portions may optionally further comprise one or more active ingredients.

[00150] In embodiments in which the shell portion or portions are prepared using a solvent-free molding process, the shell will typically comprise at least about 30 percent, e.g. at least about 45 percent by weight of a thermal-reversible carrier. The shell portion or portions may optionally further comprise up to about 55 weight percent of a release-modifying excipient. The shell portion or portions may optionally further comprise up to about 30 weight percent total of various plasticizers, adjuvants and excipients. In certain embodiments in which the shell portion is prepared by solvent-free molding, and functions to delay the release of one or more active ingredients from an underlying core portion, the release modifying excipient is preferably selected from swellable, erodible hydrophilic materials.

[00151] In embodiments in which the shell portion or portions are prepared using a solvent-based molding process, the shell portion or portions will typically comprise at least about 10 weight percent, e.g. at least about 12 weight percent or at least about 15 weight percent or at least about 20 weight percent or at least about 25 weight percent of a film-former. Here, the solvent-molded shell portion or portions may optionally further comprise up to about 55 weight percent of a release-modifying excipient. The solvent-molded shell

portion or portions may again also optionally further comprise up to about 30 weight percent total of various plasticizers, adjuvants, and excipients.

[00152] In one embodiment of this invention, the shell portion or portions of the present invention, whether prepared by a solvent-free molding process, or by a solvent-based molding process, are substantially free of pores having a diameter of 0.5-5.0 microns. As used herein, "substantially free" means that the shell portion or portions have a pore volume of less than about 0.02 cc/g, preferably less than about 0.01 cc/g, more preferably less than about 0.005 cc/g in the pore diameter range of 0.5 to 5.0 microns. In contrast, typical compressed materials have pore volumes of more than about 0.02 cc/g in this diameter range. In another embodiment of this invention, the core is a molded core and the core or core portions are substantially free of pores having a diameter of 0.5-5.0 microns.

[00153] The pore volume, pore diameter and density of the shell portions of this invention may be determined using a Quantachrome Instruments PoreMaster 60 mercury intrusion porosimeter and associated computer software program known as "Porowin." The procedure is documented in the Quantachrome Instruments PoreMaster Operation Manual. The PoreMaster determines both pore volume and pore diameter of a solid or powder by forced intrusion of a non-wetting liquid (mercury), which involves evacuation of the sample in a sample cell (penetrometer), filling the cell with mercury to surround the sample with mercury, applying pressure to the sample cell by: (i) compressed air (up to 50 psi maximum); and (ii) a hydraulic (oil) pressure generator (up to 60000 psi maximum). Intruded volume is measured by a change in the capacitance as mercury moves from outside the sample into its pores under applied pressure. The corresponding pore size diameter (d) at which the intrusion takes place is calculated directly from the so-called "Washburn Equation": $d = -$

$(4\gamma(\cos\theta))/P$ where γ is the surface tension of liquid mercury, θ is the contact angle between mercury and the sample surface and P is the applied pressure.

[00154] Equipment used for pore volume measurements:

1. Quantachrome Instruments PoreMaster 60.
2. Analytical Balance capable of weighing to 0.0001g.
3. Desiccator.

[00155] Reagents used for measurements:

1. High purity nitrogen.
2. Triply distilled mercury.
3. High pressure fluid (Dila AX, available from Shell Chemical Co.).
4. Liquid nitrogen (for Hg vapor cold trap).
5. Isopropanol or methanol for cleaning sample cells.
6. Liquid detergent for cell cleaning.

Procedure:

[00156] The samples remain in sealed packages or as received in the dessicator until analysis. The vacuum pump is switched on, the mercury vapor cold trap is filled with liquid nitrogen, the compressed gas supply is regulated at 55 psi., and the instrument is turned on and allowed a warm up time of at least 30 minutes. The empty penetrometer cell is assembled as described in the instrument manual and its weight is recorded. The cell is installed in the low pressure station and "evacuation and fill only" is selected from the analysis menu, and the following settings are employed:

Fine Evacuation time: 1 min.

Fine Evacuation rate: 10

Coarse Evacuation time: 5 min.

[00157] The cell (filled with mercury) is then removed and weighed. The cell is then emptied into the mercury reservoir, and two tablets from each sample are placed in the cell and the cell is reassembled. The weight of the cell and sample are then recorded. The cell is then installed in the low-pressure station, the low-pressure option is selected from the menu, and the following parameters are set:

Mode: Low pressure

Fine evacuation rate: 10

Fine evacuation until: 200 μ Hg

Coarse evacuation time: 10 min.

Fill pressure: Contact +0.1

Maximum pressure: 50

Direction: Intrusion And Extrusion

Repeat: 0

Mercury contact angle; 140

Mercury surface tension: 480

[00158] Data acquisition is then begun. The pressure vs. cumulative volume-intruded plot is displayed on the screen. After low-pressure analysis is complete, the cell is removed from the low-pressure station and reweighed. The space above the mercury is filled with hydraulic oil, and the cell is assembled and installed in the high-pressure cavity. The following settings are used:

Mode: Fixed rate

Motor speed: 5

Start pressure: 20

End pressure: 60,000

Direction: Intrusion and extrusion

Repeat: 0

Oil fill length: 5

Mercury contact angle: 140

Mercury surface tension: 480

[00159] Data acquisition is then begun and graphic plot pressure vs. intruded volume is displayed on the screen. After the high pressure run is complete, the low-and high-pressure data files of the same sample are merged.

[00160] The shell portion or portions of the present invention, whether prepared by a solvent-free molding process, or by a solvent-based molding process, typically has a surface gloss of at least about 150 gloss units, e.g. at least about 175 gloss units, or at least about 190 gloss units, when measured according to the method set forth below. In contrast, typical sprayed coatings have gloss values of less than about 150 gloss units. Dosage forms with high surface gloss are preferred by consumers due to their aesthetic elegance and perceived swallowability. The surface gloss of the shell depends upon a number of factors, including the shell composition, the method of forming the shell, and, if a mold is used, the surface finish on the mold.

[00161] Shell or shell portions may be tested for surface gloss using an instrument available from TriCor Systems Inc. (Elgin, IL) under the tradename TRI-COR MODEL 805A/806H SURFACE ANALYSIS SYSTEM and generally in accordance with the procedure described in "TriCor Systems WGLOSS 3.4 Model 805A/806H Surface Analysis System Reference Manual" (1996), which is incorporated by reference herein, except as modified below.

[00162] This instrument uses a CCD camera detector, a flat diffuse light source, compares tablet samples to a reference standard, and determines average gloss values at a 60 degree incident angle. During its operation, the instrument generates a gray-scale image, wherein the occurrence of brighter pixels indicates the presence of more gloss at that given location.

[00163] The instrument also incorporates software that uses a grouping method to quantify gloss: i.e., pixels with similar brightness which are grouped together for averaging purposes.

[00164] The "percent full scale" or "percent ideal" setting (also referred to as the "percent sample group" setting), is specified by the user to designate the portion of the brightest pixels above the threshold that will be considered as one group and averaged within that group. "Threshold," as used herein, is defined as the maximum gloss value that will not be included in the average gloss value calculation. Thus, the background, or the non-glossy areas of a sample are excluded from the average gloss value calculations. The method disclosed in K. Fegley and C. Vesey, "The Effect of Tablet Shape on the Perception of High Gloss Film Coating Systems," which is available at www.colorcon.com as of March 18, 2002 and incorporated by reference herein, is used to minimize the effects resulting from different tablet shapes, and to report a metric that was comparable across the industry. (The 50% sample group setting is selected as the setting which best approximates analogous data from tablet surface roughness measurements.)

[00165] After initially calibrating the instrument using a calibration reference plate (190-228; 294 degree standard; no mask, rotation 0, depth 0), a standard surface gloss measurement is created. For example, a standard surface gloss was obtained using gel-coated caplets available from McNEIL-PPC, Inc. under the tradename, EXTRA STRENGTH

TYLENOL GELCAPS. The average gloss value for a sample of 112 of such gel-coated caplets was then determined, while employing the 25 mm full view mask (190-280), and configuring the instrument to the following settings:

Rotation: 0

Depth: 0.25 inches

Gloss Threshold: 95

% Full Scale: 50%

Index of Refraction: 1.57

The average surface gloss value for the reference standard was determined to be 269.

[00166] The total weight of the shell portion or portions is preferably about 20 percent to about 400 percent of the weight of the core. In embodiments wherein the shell portion or portions prepared by a solvent-free molding process, the total weight of the shell portion or portions is typically from about 50 percent to about 400 percent, e.g. from about 75 percent to about 400 percent, or about 100 percent to about 200 percent of the weight of the core. In embodiments wherein the shell portion or portions are prepared by a solvent-based molding process, the total weight of the shell portion or portions is typically from about 20 percent to about 100 percent of the weight of the core.

[00167] Typical shell portion thicknesses which may be employed in this invention are about 50 to about 4000 microns. In certain preferred embodiments, the shell has a thickness of less than 800 microns. In embodiments wherein the shell portion is prepared by a solvent-free molding process, the shell portion typically has a thickness of about 500 to about 4000 microns, e.g. about 500 to about 2000 microns, say about 500 to about 800 microns, or about 800 to about 1200 microns. In embodiments wherein the shell portion is prepared by a solvent-based molding process, the shell portion typically has a thickness of less than about

800 microns, e.g. about 100 to about 600 microns, say about 150 to about 400 microns. In a particularly preferred embodiment the dosage form comprises first and second core portions and first and second shell portions, and at least one of the shell portions has a thickness of less than about 800 microns, e.g. about 100 to about 600 microns, e.g. about 150 to about 400 microns

[00168] Suitable thermal-reversible carriers for making the core, or the shell, or a portion thereof, by molding are thermoplastic materials typically having a melting point below about 110°C, more preferably between about 20 and about 100°C. Examples of suitable thermal-reversible carriers for solvent-free molding include thermoplastic polyalkylene glycols, thermoplastic polyalkylene oxides, low melting hydrophobic materials, thermoplastic polymers, thermoplastic starches, and the like. Preferred thermal-reversible carriers include polyethylene glycol and polyethylene oxide. Suitable thermoplastic polyalkylene glycols for use as thermal-reversible carriers include polyethylene glycol having molecular weight from about 100 to about 20,000, e.g. from about 100 to about 8,000 Daltons. Suitable thermoplastic polyalkylene oxides include polyethylene oxide having a molecular weight from about 100,000 to about 900,000 Daltons. Suitable low-melting hydrophobic materials for use as thermal-reversible carriers include fats, fatty acid esters, phospholipids, and waxes which are solid at room temperature, fat-containing mixtures such as chocolate; and the like. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl trilaurylate, glyceryl myristate, GlycoWax-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include

phosphotidyl choline, phosphotidyl serine, phosphotidyl inositol, and phosphotidic acid. Examples of suitable waxes which are solid at room temperature include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax. Suitable thermoplastic polymers for use as thermal-reversible carriers include thermoplastic water swellable cellulose derivatives, thermoplastic water insoluble polymers, thermoplastic vinyl polymers, thermoplastic starches, and thermoplastic resins, and combinations thereof. Suitable thermoplastic water swellable cellulose derivatives include include hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), carboxymethylcellulose (CMC), cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxybutylcellulose (HBC), hydroxyethylcellulose (HEC), hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose, and salts, derivatives, copolymers, and combinations thereof. Suitable thermoplastic water insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers, and the like and derivatives, copolymers, and combinations thereof. Suitable thermoplastic vinyl polymers include polyvinylacetate, polyvinyl alcohol, and polyvinyl pyrrolidone (PVP). Examples of suitable thermoplastic starches for use as thermal-reversible carriers are disclosed for example in U.S. Patent No. 5,427,614._____. Examples of suitable thermoplastic resins for use as thermal-reversible carriers include dammars, mastic, rosin, shellac, sandarac, and glycerol ester of rosin. In one embodiment, the thermal-reversible carrier for making the core, or a portion thereof, by molding is selected from polyalkylene glycols, polyalkaline oxides, and combinations thereof.

[00169] Suitable release-modifying excipients for making the core, or the shell, or a portion thereof, by solvent free or solvent based molding include but are not limited to swellable erodible hydrophilic materials, pH-dependent polymers, pore formers, and

insoluble edible materials. In one embodiment, suitable release-modifying excipients for making the core, or the shell, or a portion thereof, by molding include hydroxypropylmethylcellulose, polyethylene oxide, ammonio methacrylate copolymer type B, and shellac, and combinations thereof.

[00170] Suitable swellable erodible hydrophilic materials for use as release-modifying excipients for making the core, or the shell, or a portion thereof by a solvent-free molding process include water swellable cellulose derivatives, polyalkylene glycols, thermoplastic polyalkylene oxides, acrylic polymers, hydrocolloids, clays, gelling starches, and swelling cross-linked polymers, and derivatives, copolymers, and combinations thereof. Examples of suitable water swellable cellulose derivatives include sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxyphenylcellulose, hydroxyethylcellulose (HEC), hydroxypentylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, hydroxypropylethylcellulose. Examples of suitable polyalkylene glycols include polyethylene glycol. Examples of suitable thermoplastic polyalkylene oxides include poly(ethylene oxide). Examples of suitable acrylic polymers include potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, CARBOPOL (high-molecular weight cross-linked acrylic acid homopolymers and copolymers), and the like. Examples of suitable hydrocolloids include alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pustulan, laminarin, scleroglucan, gum arabic, inulin, pectin, gelatin, whey, rhamnan, zooglan, methylcellulose, chitin, cyclodextrin, chitosan. Examples of suitable clays include smectites such as bentonite, kaolin, and laponite; magnesium trisilicate, magnesium aluminum silicate, and the like, and derivatives and mixtures thereof. Examples

of suitable gelling starches include acid hydrolyzed starches, swelling starches such as sodium starch glycolate, and derivatives thereof. Examples of suitable swelling cross-linked polymers include cross-linked polyvinyl pyrrolidone, cross-linked agar, and cross-linked carboxymethylcellulose sodium.

[00171] Suitable pH-dependent polymers for use as release-modifying moldable excipients for making the molded matrix or molded core or molded shell or a portion thereof by molding include enteric cellulose derivatives, for example hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate; natural resins such as shellac and zein; enteric acetate derivatives such as for example polyvinylacetate phthalate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate; and enteric acrylate derivatives such as for example polymethacrylate-based polymers such as poly(methacrylic acid, methyl methacrylate) 1:2, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT S, and poly(methacrylic acid, methyl methacrylate) 1:1, which is commercially available from Rohm Pharma GmbH under the tradename EUDRAGIT L, and the like, and derivatives, salts, copolymers, and combinations thereof.

[00172] Suitable insoluble edible materials for use as release-modifying excipients making the core, or the shell, or a portion thereof by molding, include water-insoluble polymers, and low-melting hydrophobic materials. Examples of suitable water-insoluble polymers include ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers; and the like and derivatives, copolymers, and combinations thereof. Suitable low-melting hydrophobic materials include fats, fatty acid esters, phospholipids, and waxes. Examples of suitable fats include hydrogenated vegetable oils such as for example cocoa butter,

hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil; and free fatty acids and their salts. Examples of suitable fatty acid esters include sucrose fatty acid esters, mono, di, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurylate, glyceryl myristate, GlycoWax-932, lauroyl macrogol-32 glycerides, and stearyl macrogol-32 glycerides. Examples of suitable phospholipids include phosphotidyl choline, phosphotidyl serene, phosphotidyl enositol, and phosphotidic acid. Examples of suitable waxes include carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; and the like.

[00173] Suitable pore formers for use as release-modifying excipients for making the molded matrix, the core, the shell, or a portion thereof by molding include water-soluble organic and inorganic materials. In one embodiment the pore former is hydroxypropylmethylcellulose. Examples of suitable water-soluble organic materials include water soluble polymers including water soluble cellulose derivatives such as hydroxypropylmethylcellulose, and hydroxypropylcellulose; water soluble carbohydrates such as sugars, and starches; water soluble polymers such as polyvinylpyrrolidone and polyethylene glycol, and insoluble swelling polymers such as microcrystalline cellulose. Examples of suitable water soluble inorganic materials include salts such as sodium chloride and potassium chloride and the like and/or mixtures thereof.

[00174] In embodiments in which the first or second shell portion comprises an active ingredient intended to have immediate release from the dosage form, the shell portion is preferably prepared via the solvent-free molding method described above. In such embodiments the thermal-reversible carrier is preferably selected from polyethylene glycol

with weight average molecular weight from about 1450 to about 20000, polyethylene oxide with weight average molecular weight from about 100,000 to about 900,000, and the like.

[00175] In embodiments in which at least one of the first or second shell portions function to confer modified release properties to at least one active ingredient contained within the dosage form, in the core, the shell or both, the shell portion typically comprises at least one release modifying agent as described above.

[00176] In embodiments of the invention in which the core portions and shell portions each comprise a dose of active ingredient, the dosage form may function for example as a multi-compartment, e.g. a four-compartment pulsatile release delivery system. In one such embodiment, each of the compartments may comprise a dose of the same active ingredient, to be release at a desired time or rate. In another such embodiment, the corresponding first core portion and first shell portions may comprise a dose of the same first active ingredient to be released at a desired time or rate, while the second core portion and second shell portion may comprise a dose of the same second active ingredient to be released at a desired time or rate. In such embodiments, each compartment comprises inactive materials which enable the desired functionality of that particular core portion or shell portion.

[00177] In certain such embodiments, the dosage form may further comprise a water-impermeable barrier layer between the first and second core portions. The water-impermeable barrier layer may be made by any method, for example compression or molding, and preferably comprises at least one water-insoluble material selected from water-insoluble polymers, insoluble edible materials, pH-dependent polymers, and mixtures thereof.

[00178] In one particular embodiment of this invention, at least one active ingredient contained within the dosage form exhibits a delayed burst release profile. By "delayed burst release profile" it is meant that the release of that particular active ingredient from the dosage

form is delayed for a pre-determined time after ingestion by the patient, and the delay period ("lag time") is followed by prompt (immediate) release of that active ingredient. At least one shell portion of the present invention provides for the delay period and is preferably substantially free of the active ingredient to be released in a delayed burst manner. In such embodiments, the delayed burst active ingredient is typically contained within the corresponding underlying core portion. In these embodiments, the core portion may be prepared by compression or molding, and is formulated for immediate release, as is known in the art, so that the core portion is readily soluble upon contact with the dissolution medium. In such embodiments the core portion preferably comprises a disintegrant, and optionally comprises additional excipients such as fillers or thermoplastic materials selected from water-soluble or low-melting materials, and surfactants or wetting agents. In these embodiments, the dissolution of the burst release active ingredient, after the delay period, meets USP specifications for immediate release tablets containing that active ingredient. For example, for acetaminophen tablets, USP 24 specifies that in pH 5.8 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the acetaminophen contained in the dosage form is released therefrom within 30 minutes after dosing, and for ibuprofen tablets, USP 24 specifies that in pH 7.2 phosphate buffer, using USP apparatus 2 (paddles) at 50 rpm, at least 80% of the ibuprofen contained in the dosage form is released therefrom within 60 minutes after dosing. See USP 24, 2000 Version, 19 – 20 and 856 (1999).

[00179] In another particular embodiment of this invention at least one active ingredient contained within the dosage form exhibits a delayed and sustained release profile. By "delayed then sustained release profile" it is meant that the release of that particular active ingredient from the dosage form is delayed for a pre-determined time after ingestion by the patient, and the delay period ("lag time") is followed by sustained (prolonged, extended, or retarded) release of that active ingredient. At least one shell portion of the present invention

provides for the delay period, and is preferably substantially free of the active ingredient to be released in a delayed then sustained manner. In such embodiments, the delayed then sustained release active ingredient is preferably contained within the corresponding underlying core portion. In such embodiments the core portion may function for example as an eroding matrix or a diffusional matrix, or an osmotic pump. In embodiments in which the core portion functions as a diffusional matrix through which active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore-formers. Alternately, in such embodiments in which the core portion is prepared by molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated. In embodiments in which the core portion functions as an eroding matrix from which dispersed active ingredient is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, and combinations thereof.

[00180] In embodiments in which one or more core portions function as a diffusional matrix through which active ingredient contained therein is liberated in a sustained, extended, prolonged, or retarded manner, the core portion preferably comprises a release-modifying excipient selected from combinations of insoluble edible materials and pore formers. Alternately, in such embodiments in which the core portion is prepared by solven-free molding, the thermal-reversible carrier may function by dissolving and forming pores or channels through which the active ingredient may be liberated.

[00181] In embodiments in which the core or a portion thereof functions as an eroding matrix from which dispersed active ingredient is liberated in a sustained, extended,

prolonged, or retarded manner, the core portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, insoluble edible materials, and combinations thereof. In such embodiments, the overlaying shell portion will typically be breached or dissolved prior to onset of erosion of the underlying core portion, and release of active ingredient therefrom.

[00182] In embodiments in which a shell portion functions by an erosion-based mechanism to provide a time delay for the release of an active ingredient from an underlying core portion, the release-delaying shell portion preferably comprises a release modifying excipient selected from swellable erodible hydrophilic materials, insoluble edible materials, and combinations thereof.

[00183] In embodiments in which a shell portion functions as an eroding matrix from which active ingredient dispersed therein is liberated in a sustained, extended, prolonged, or retarded manner, the shell portion preferably comprises a release-modifying compressible or moldable excipient selected from swellable erodible hydrophilic materials, pH-dependent polymers, insoluble edible materials, and combinations thereof.

[00184] In embodiments of the invention, in which a shell portion functions to confer a delay to the release of one or more active ingredients contained in an underlying core portion, the release-delaying shell portion preferably provides a delay of greater than one hour, for example at least about 3 hours, or at least about 4 hours, or at least about 6 hours, or at least about 12 hours to the onset of dissolution of the active ingredient upon contacting of the dosage form with a liquid medium such as water, gastrointestinal fluid or the like. The delay period is typically controlled by the shell portion thickness, composition, or a combination thereof. In one embodiment the delay period is independent of the pH of the dissolution media or fluid environment. For example, the average lag-time for dissolution of active

ingredient in 0.1 N HCl is not substantially different (i.e. within about 30 minutes, preferably within about 15 minutes) from the average lag-time for the dissolution of active ingredient in pH 5.6 buffer system. In certain such embodiments, the release-delaying shell portion preferably comprises a release modifying excipient selected from swellable erodible hydrophilic materials, insoluble edible materials, and combinations thereof.

[00185] In embodiments in which one or more shell portions contain active ingredient which is released essentially immediately upon ingestion of the dosage form, the shell portion preferably comprises materials which exhibit rapid dissolution in gastro-intestinal fluids. For example the immediate release shell portion or portions may comprise readily soluble materials selected from water soluble or water swellable thermoplastic film formers, water soluble or water swellable thickeners, crystallizable and non-crystallizable carbohydrates. In certain such embodiments, suitable water soluble or water swellable thermoplastic film formers may be selected from water swellable cellulose derivatives, thermoplastic starches, polyalkylene glycols, polyalkylene oxides, and amorphous sugar glass, and combinations thereof. In certain other such embodiments, suitable film formers may be selected from film forming water soluble polymers such as for example water soluble vinyl polymers, water soluble polycarbohydrates, water swellable cellulose derivatives, and water soluble copolymers; film-forming proteins, and combinations thereof. In certain other such embodiments, suitable thickeners may be selected from gelling polymers or hydrocolloids; gelling starches, and crystallizable carbohydrates. In certain other such embodiments, suitable non-crystallizable carbohydrates may be selected from polydextrose, starch hydrolysates, and non-crystallizable sugar alcohols. In such embodiments, the immediate release shell portion will preferably be breached or dissolved within 30 minutes in 900 ml water or 0.1 N HCl, or phosphate buffer solution at 37°C with stirring by a USP type 2 (Paddle method) at 50 or 100 rpm.

[00186] In one embodiment of the invention, the shell portion or portions additionally comprise at least one active ingredient which may be the same or different than the active ingredient contained in the core.

[00187] In embodiments in which the first or second shell portions confer sustained, extended, or retarded release of an active ingredient contained in an underlying core or core portion, the release-modifying agent in said shell portion preferably comprises a pore-former, and optionally a film-former. In a particularly preferred embodiment, the shell portion functions as a diffusional membrane. In some such embodiments, the dissolution of the active ingredient may follow "diffusion-controlled" release kinetics, as described for example in Example 1 of U.S. Patent No. 5,286,497. Shell portions which confer sustained, extended, or retarded release and/or function as diffusional membranes can be prepared by a solvent-free method, or a solvent-based method, as described above.

[00188] In embodiments in which the first or second shell portions confer sustained, extended, or retarded release of an active ingredient contained in said first or second shell portion, the release-modifying agent in said shell portion preferably comprises a swellable erodible hydrophilic material, and may optionally comprise a secondary gelling agent such as for example cross-linked carboxymethylcellulose, cross-linked polyvinylpyrrolidone, or sodium starch glycolate.

[00189] In embodiments in which the first or second shell portions confer a delayed release to an active ingredient contained in an underlying core or core portion, the release-modifying agent is preferably selected from swellable erodible hydrophilic materials. Shell portions which confer delayed release can be prepared by a solvent-free method, or a solvent-based method, as described above.

[00190] In embodiments in which the first or second shell portions provide a barrier to prevent release therethrough of an active ingredient contained in the underlying core or core portion, the shell portion is preferably prepared via a solvent-free molding method, as described above. In such embodiments, the thermal-reversible carrier is preferably selected from waxes, such as for example carnuba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; hydrogenated vegetable oils such as for example cocoa butter, hydrogenated castor oil; other waxy materials such as for example glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl triaurylate, glyceryl myristate; thermal-reversible polymers such as for example polycaprolactones and polyvinyl acetate.. In certain embodiments, an impermeable barrier can be formed which consists essentially of the thermal reversible carrier. In such embodiments, an additional release-modifying agent is not necessary. In certain other embodiments, the release-modifying agent is preferably selected from water insoluble polymers such as cellulose acetate, acrylates, acrylic acid copolymers, cellulose acetate, cellulose acetate propionate, cellulose acetate propionate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, acetaldehyde dimethylcellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, ethylcellulose, methacrylates, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, and the like , and mixtures thereof. In such embodiments, the shell portion may optionally further comprise a liquid carrier such as for example mineral oil, propylene glycol, low molecular weight polyethylene glycol, glycerin, and the like.

[00191] In one embodiment of the invention, the core, the shell, a core portion, or a shell portion is made by the thermal setting molding method and apparatus described in copending U.S. patent application Serial No. 09/966,450, pages 57-63, the disclosure of which is incorporated herein by reference. In this embodiment, the core, the shell, or a

portion thereof is formed by injecting a starting material in flowable form into a molding chamber. The starting material preferably comprises an active ingredient and a thermal setting material at a temperature above the melting point of the thermal setting material but below the decomposition temperature of the active ingredient. The starting material is cooled and solidifies in the molding chamber into a shaped form (i.e., having the shape of the mold).

[00192] According to this method, the starting material must be in flowable form. For example, it may comprise solid particles suspended in a molten matrix, for example a polymer matrix. The starting material may be completely molten or in the form of a paste. The starting material may comprise an active ingredient dissolved in a molten material. Alternatively, the starting material may be made by dissolving a solid in a solvent, which solvent is then evaporated from the starting material after it has been molded.

[00193] The starting material may comprise any edible material which is desirable to incorporate into a shaped form, including active ingredients, nutritionals, vitamins, minerals, flavors, sweeteners, and the like. Preferably, the starting material comprises an active ingredient and a thermal setting material. The thermal setting material may be any edible material that is flowable at a temperature between about 37 and about 120°C, and that is a solid at a temperature between about 0 and about 35°C. Preferred thermal setting materials include water-soluble polymers such as polyalkylene glycols, polyethylene oxides and derivatives, and sucrose esters; fats such as cocoa butter, hydrogenated vegetable oil such as palm kernel oil, cottonseed oil, sunflower oil, and soybean oil; mono-, di-, and triglycerides, phospholipids, waxes such as carnuba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate; sugar in the form on an amorphous glass such as that used to make hard candy forms, sugar in a supersaturated solution such as that used to make fondant forms; low-moisture polymer

solutions such as mixtures of gelatin and other hydrocolloids at water contents up to about 30% such as those used to make "gummi" confection forms. In a particularly preferred embodiment, the thermal setting material is a water-soluble polymer such as polyethylene glycol.

[00194] In another embodiment of the invention, the core, the shell, a core portion, or a shell portion is made using the thermal cycle molding method and apparatus described in copending U.S. patent application Serial No. 09/966,497, pages 27-51, the disclosure of which is also incorporated herein by reference. In the thermal cycle molding method and apparatus of U.S. patent application Serial No. 09/966,497, a thermal cycle molding module having the general configuration shown in Figure 3 therein is employed. The thermal cycle molding module 200 comprises a rotor 202 around which a plurality of mold units 204 are disposed. The thermal cycle molding module includes a reservoir 206 (see Figure 4) for holding flowable material to make the core, the shell, a core portion, or a shell portion. In addition, the thermal cycle molding module is provided with a temperature control system for rapidly heating and cooling the mold units. Figures 55 and 56 depict such a temperature control system 600.

[00195] This invention will be illustrated by the following examples, which are not meant to limit the invention in any way.

Example 1

[00196] Dosage forms according to the invention comprising a core within a shell comprising a first shell portion and a second shell portion were prepared as follows.

[00197] The following ingredients were used to make the cores:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/dosage Form
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Verapamil HCL Extended Release Pellets	Verelan PM 300mg capsules	Schwarz Pharma, Inc., Gainesville, GA	22.0	131
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	47.0	279
Shellac Powder		Mantrose-Haeuser Company, Attetboro, MA	10.0	59
Croscarmellose Sodium	Ac-Di-Sol®	FMC Corporation, Newark, DE	21.0	125

[00198] The cores were prepared as follows: a beaker was submersed in a 70°C water bath (Ret digi-visc; Antal-Direct, Wayne, PA). The polyethylene glycol (PEG) was added to the beaker and mixed with a spatula until melted. The shellac powder was screened through a #40 mesh screen, and then added to the molten PEG. The combined ingredients were mixed until all the powder was dispersed. Croscarmellose sodium was added next and the beaker contents were mixed for an additional two minutes. The verapamil HCL pellets were then added, and the contents were mixed for five more minutes. Cores were made by dispensing 620 to 640 mg of the resulting molten mixture into an open stainless steel mold (round, 0.4455 inch diameter) and closing the mold. The finished cores were ejected from the mold.

[00199] The first shell portion was made using the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Pseudoephedrine HCl Crystal		BASF PharmaChemikalien GmbH & Co. Ludwigshafen/Rhein.	30.0	53
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	50.0	89
Polyethylene Oxide (MW 200,000)	Polyox® WSR N-80	Union Carbide Corporation, Danbury, CT	15.0	27
Triethyl Citrate		Morflex, Inc., Greensboro, NC	5.0	9

[00200] The first shell portion material was prepared by first submersing a beaker in a 70°C water bath (Ret digi-visc; Antal-Direct, Wayne, PA). The polyethylene glycol (PEG) was added to the beaker and mixed with a spatula until melted. The triethyl citrate was then added to the molten PEG and the mixture was mixed for one minute. The polyethylene oxide (PEO) was added thereto, and the ingredients were mixed for 10 additional minutes. The pseudoephedrine hydrochloride was added, and the ingredients were mixed for two more minutes. The first shell portion material was provided in flowable form.

[00201] The second shell portion was made using the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Dextromethorphan HBr		Roche Chemical Co., Belvidere, NJ	10.0	16
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	50.0	77
Polyethylene Oxide (MW 200,000)	Polyox® WSR N-80	Union Carbide Corporation, Danbury, CT	15.0	23
Shellac Powder		Mantrose-Haeuser Company, Attetboro, MA	10.0	16
Croscarmellose Sodium	Ac-Di-Sol®	FMC Corporation, Newark, DE	5.0	8
Triethyl Citrate		Morflex, Inc., Greensboro, NC	10.0	16

[00202] The second shell portion material was prepared by first submersing a beaker in a 70°C water bath (Ret digi-visc; Antal-Direct, Wayne, PA). PEG was added to the beaker and mixed with a spatula until melted. The shellac powder was screened through a #40 mesh screen, and then added to the molten PEG. The combined ingredients were mixed until all powder was dispersed. The triethyl citrate was added next and the beaker contents were mixed for one minute. PEO was added to the beaker and the mixture was mixed for 10 minutes. Croscarmellose sodium was then added and the contents of the beaker were mixed

for two additional minutes. Finally, dextromethorphan HBr was added to the beaker and the ingredients were mixed for two more minutes. The second shell portion material was provided in flowable form.

[00203] A laboratory scale thermal cycle molding unit was used to apply the first and second shell portions to the cores, and comprised a single mold assembly made from an upper mold assembly portion comprising an upper mold cavity, and a lower mold assembly portion comprising a lower mold cavity. The lower mold assembly portion was first cycled to a hot stage at 85°C for 30 seconds. The first shell portion material of Example 1 was introduced into the lower mold cavity. A core prepared as described above was then inserted into the cavity. A blank upper mold assembly portion was mated with the lower mold assembly portion. The mold assembly was then cycled to a cold stage at 5°C for 60 seconds to harden the first shell portion. The blank mold assembly portion was removed from the lower mold assembly portion, and the half-coated core was ejected from the lower mold cavity. The "weight gain" due to the first shell portion (i.e. the difference in weight between the half-coated core and the uncoated core) was recorded.

[00204] The upper mold assembly portion was cycled to a hot stage at 85°C for 30 seconds. The second shell portion material was added to the upper mold cavity. The half-coated core was then inserted into the upper mold cavity such that the uncoated portion of the core rested within the upper mold cavity. The lower mold assembly portion, which had been maintained at 5°C, was then mated with the upper mold assembly portion. The upper mold assembly portion was then cycled to a cold stage at 5°C for 60 seconds to harden the second shell portion. The lower mold assembly portion was then removed and the finished dosage form, a molded core coated with two different shell portions, was ejected from the

upper mold cavity. The weight gain due to the second shell portion (i.e. the difference in weight between the finished dosage form, and the half-coated core) was recorded.

[00205] The release profiles for the three active ingredients contained in the dosage form of Example 1 were compared with those of other dosage forms containing the same active ingredients. The results are shown in Fig. 3, which depicts the percent release of active ingredient versus hours for the dosage form of Example 1 and the other dosage forms. Curve (a) depicts the dissolution profile of the verapamil HCL contained in the core of the dosage form of this example. Curve (b) depicts the dissolution of verapamil from commercially available, sustained release capsules (Verelan® PM 300mg). Curve (c) shows the dissolution of dextromethorphan HBr contained in the second shell portion of the dosage form of this example. Curve (d) shows the dissolution profile of pseudoephedrine HCl contained in the first shell portion of the dosage form of this example. Curve (e) depicts the dissolution profile of pseudoephedrine HCl from commercially available immediate release tablets (Sudafed®). Curve (f) depicts the dissolution profile of dextromethorphan HBr from commercially available immediate release coated tablets (Tylenol® Cold caplets).

[00206] All curves were derived using the following dissolution apparatus: USP Type II apparatus (paddles, 50 RPM). Media: pH 7.2 phosphate buffer at 37°C. Time points: Samples were removed at 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 hours to be analyzed for pseudoephedrine HCl, dextromethorphan HBr, and verapamil HCl. Dissolution samples were analyzed for these three active ingredients versus a standard prepared at the theoretical concentration for 100% released of each compound. Samples were analyzed using an HPLC equipped with a Waters® 717 Autoinjector and a Waters® 486 UV detector set at a wavelength of 214 nm. The mobile phase was prepared using 55% acetonitrile and 45% 18 mM Potassium phosphate buffer. The injection volume was 50 µL with a run time of

approximately 8 minutes at a pump flow of 2.0 mL/min. A Zorbax® 300-SCX (4.6m x 25 cm) column was used.

[00207] The curves depicted in Figure 3 demonstrate that the verapamil HCl was released from the dosage form of the present example in a sustained manner. The dextromethorphan HBr was released from the dosage form of the present example in a delayed manner. The pseudoephedrine HCl was immediately released from the dosage form of the present example.

Example 2

[00208] Dosage forms according to the invention comprising a core having a first core portion and a second core portion within a shell having a first shell portion and a second shell portion were prepared as follows.

[00209] The following ingredients were used to make the first core portion:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Pseudoephedrine HCl Crystal		BASF PharmaChemikalien GmbH & Co. Ludwigshafen/Rhein.	15.0	48
Polyethylene Oxide (MW 300,000)	Polyox® WSR N-750	Union Carbide Corporation, Danbury, CT	75.0	239
Hydroxypropyl Methylcellulose	Methocel E5	Dow Chemical Company, Midland, MI	8.5	27
Magnesium Stearate		Mallinckrodt Inc., St. Louis, MO	1.5	5
Alcohol USP (dried as solvent)				

[00210] The pseudoephedrine HCl crystal, hydroxypropyl methylcellulose, and PEO (MW=300,000), were first mixed in a plastic bag for 1-2 minutes. This powder mixture was added into the (5 qt) bowl of a planetary mixer (Hobart Corp., Dayton, OH). The alcohol was

added to the powder mixture while mixing at low speed. The ingredients were mixed for 10 minutes. The resulting granulation was removed from the bowl and dried at room temperature for 12 to 16 hours to remove all residual solvent. The granulation was screened through a #20 mesh screen and were put into a plastic bag. Magnesium stearate was added to the dry granules, followed by mixing for 3 minutes to form the first core portion.

[00211] The following ingredients were used to make the second core portion:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Dextromethorphan HBr		Roche Chemical Co. Belvidere, NJ	15.1	48
Polyethylene Oxide (MW 300,000)	Polyox® WSR N-750	Union Carbide Corporation, Danbury, CT	75.4	240
Hydroxypropyl Methylcellulose	Methocel E5	Dow Chemical Company, Midland, MI	8.5	27
Magnesium Stearate		Mallinckrodt Inc., St. Louis, MO	1.0	3
D&C Yellow #10			Trace Amount	
Ethanol Anhydrous (dried as solvent)				

[00212] Dextromethorphan HBr, hydroxypropyl methylcellulose, PEO (MW=300,000), and D&C yellow #10 were mixed in a plastic bag for 1-2 minutes. This powder mixture was added into the (5 qt) bowl of a planetary mixer (Hobart Corp., Dayton, OH). The alcohol was added to the powder mixture while mixing at low speed. The ingredients were mixed for 10 minutes. The resulting granulation was removed from the bowl and dried at room temperature for 12 to 16 hours to remove all residual solvent. The granulation was screened through a #20 mesh screen and were put into a plastic bag. Magnesium stearate was added to the dry granules, followed by mixing for 3 minutes to form the second core portion.

[00213] Cores were made from equal portions (by weight) of the first and second core portions as follows. A model M hydraulic Carver Laboratory Press (Fred S. Carver, Inc., Hydraulic Equipment, Summit, NJ) was employed. A round, concave punch and die unit having 0.4455" diameter was used for compression. The pseudoephedrine granulation for the first core portion was fed into the cavity mold of the press and was gently tapped. Then the dextromethorphan granulation for the second core portion was fed into the cavity overlying the pseudoephedrine granulation. The granulations were pressed into a solid two-portion core using 1500 lb/sq. in. of compression force.

[00214] The first shell portion was made using the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Cellulose Acetate 398-10		Eastman Chemical Company, Kingsport, TN	60.0	12.9
Polyethylene Oxide (MW 200,000)	Polyox [®] WSR N-80	Union Carbide Corporation, Danbury, CT	20.0	4.3
Hydroxypropyl Methylcellulose	Methocel E5	Dow Chemical Company, Midland, MI	20.0	4.3
Acetone (dried as solvent)				

[00215] The cellulose acetate was added to a beaker containing acetone and mixed using a mixer until all powder was dissolved. An agitating speed of 500 rpm was used. Hydroxypropyl methylcellulose and PEO, which were screened through a #40 mesh screen, were added to the cellulose acetate solution, which was again mixed until all powder was dispersed. The first shell portion material was provided in flowable form.

[00216] The second shell portion was made using the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Cellulose Acetate 398-10		Eastman Chemical Company, Kingsport, TN	56.0	12.0

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Ammonio Methacrylate Copolymer Type B	Eudragit® RS 100	Roehm America Inc., Somerset, NJ	24.0	5.2
Polyethylene Oxide (MW 200,000)	Polyox® WSR N-80	Union Carbide Corporation, Danbury, CT	20.0	4.3
Acetone (dried as solvent)				

[00217] The cellulose acetate was added into a beaker containing acetone and was mixed using a mixer until all powder was dissolved. An agitating speed of 500 rpm was used. Ammonio methacrylate copolymer and PEO, which were screened through a #40 mesh screen, were added to the cellulose acetate solution, which was then mixed until all powder was dispersed. The second shell portion was provided in flowable form.

[00218] A thermal cycle molding module as described in Example 1 was used to apply the first and second shell portions onto the core. The lower mold assembly portion was first cycled to a cold stage at 25°C for 30 seconds. The first shell portion material was added to the lower mold cavity. A two-portion core as described above was inserted into the lower mold cavity such that the first core portion, containing pseudoephedrine HCl sustained release granules, was inserted into the lower mold cavity. A blank upper mold assembly portion was mated the lower mold assembly portion. The mold assembly was then cycled to a hot stage at 85°C for 2 minutes. Next, the assembly was cycled to a cold stage at 5°C for 1 minute to harden the first shell portion. The blank upper mold assembly portion was then removed from the lower mold assembly portion.

[00219] The upper mold assembly portion was next cycled to a cold stage at 25°C for 30 seconds. The second shell portion material was added to the upper mold cavity. The half-coated core, with the first shell portion, was inserted into the upper mold cavity such that the uncoated core portion containing dextromethorphan HBr sustained release granules rested

within the upper mold cavity. The lower mold assembly portion, which had been maintained at 5°C, was then mated with the upper mold assembly portion. The upper mold assembly portion was then cycled to a hot stage at 85°C for 2 minutes, followed by a cold stage at 5°C for 1 minute to harden the second shell portion. The lower mold assembly portion was removed and the finished dosage form, a two-portion core coated with two different shell portions, was ejected from the upper mold cavity. The weight gain due to the first and second shell portions, i.e. the difference in weights of the finished dosage form and the uncoated core, was recorded. The finished dosage form was dried at room temperature for 24 hours to remove all residual solvent.

[00220] The release profiles for the two active ingredients contained in the dosage form of this example were compared with those of other dosage forms containing the same active ingredients. The results are shown in Fig. 4, which depicts the percent release of active ingredient versus hours for the dosage form of Example 2 and other dosage forms. Curve (a) depicts the dissolution profile of the dextromethorphan HBr contained in the second core portion of the finished dosage form of this example. Curve (b) depicts the dissolution profile of the dextromethorphan HBr from the uncoated core prepared according to this example, but without the second shell portion. Curve (c) shows the dissolution profile of pseudoephedrine HCl contained in the first core portion of the finished dosage form of this Example. Curve (d) shows the dissolution profile of pseudoephedrine HCl from the uncoated core prepared according to this example, but without the first shell portion.

[00221] All curves were derived using the following dissolution apparatus: USP Type II apparatus (paddles, 50 RPM). Media: pH 7.2 phosphate buffer at 37°C. Time points: Samples were removed at 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 hours to be analyzed for pseudoephedrine HCl, and dextromethorphan HBr. Dissolution samples were analyzed for

these two active ingredients versus a standard prepared at the theoretical concentration for 100% released of each compound. Samples were analyzed using an HPLC equipped with a Waters® 717 Autoinjector and a Waters® 486 UV detector set at a wavelength of 214 nm. The mobile phase was prepared using 55% acetonitrile and 45% 18mM Potassium phosphate buffer. The injection volume was 50 µL with a run time of approximately 8 minutes and a pump flow of 2.0 mL/min. A Zorbax® 300-SCX (4.6m x 25 cm) column was used.

Example 3

[00222] Dosage forms of the invention are made in a continuous process using an apparatus comprising two thermal cycle molding modules linked in series via a transfer device as described at pages 14-16 of copending U.S. Application Serial No. 09/966,939, the disclosure of which is incorporated herein by reference. The dosage forms comprise a core coated with a shell comprising a first portion and a second portion.

[00223] The core is made of a core flowable material comprising the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/dosage Form
Verapamil HCL Extended Release Pellets	Verelan PM 300mg capsules	Schwarz Pharma, Inc., Gainesville, GA	22.0	131
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	47.0	279
Shellac Powder		Mantrose-Haeuser Company, Attleboro, MA	10.0	59
Croscarmellose Sodium	Ac-Di-Sol®	FMC Corporation, Newark, DE	21.0	125

[00224] PEG is heated to 70°C and mixed until melted. The shellac powder is screened through a #40 mesh screen, and then added to the molten PEG. The combined ingredients are mixed until all the powder is dispersed. Croscarmellose sodium is added next

and the ingredients are mixed for an additional two minutes. The verapamil HCL pellets are then added, and the ingredients are mixed for five more minutes.

[00225] The first shell portion is made of a first shell portion flowable material comprising the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Pseudoephedrine HCl Crystal		BASF PharmaChemikalien GmbH & Co. Ludwigshafen/Rhein.	30.0	53
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	50.0	89
Polyethylene Oxide (MW 200,000)	Polyox® WSR N-80	Union Carbide Corporation, Danbury, CT	15.0	27
Triethyl Citrate		Morflex, Inc., Greensboro, NC	5.0	9

[00226] The PEG is heated to 70°C and mixed until melted. The triethyl citrate is then added to the molten PEG and the mixture is mixed for one minute. The PEO is added thereto, and the ingredients are mixed for 10 additional minutes. The pseudoephedrine hydrochloride is added, and the ingredients are mixed for two more minutes.

[00227] The second shell portion is made of a second shell portion flowable material comprising the following ingredients:

Ingredient	Trade Name	Manufacturer	Weight %	Mg/Dosage Form
Dextromethorphan HBr		Roche Chemical Co., Belvidere, NJ	10.0	16
Polyethylene Glycol 3350	Carbowax®	Union Carbide Corporation, Danbury, CT	50.0	77
Polyethylene Oxide (MW 200,000)	Polyox® WSR N-80	Union Carbide Corporation, Danbury, CT	15.0	23
Shellac Powder		Mantrose-Hauser	10.0	16

		Company, Attleboro, MA		
Croscarmellose Sodium	Ac-Di-Sol®	FMC Corporation, Newark, DE	5.0	8
Triethyl Citrate		Morflex, Inc., Greensboro, NC	10.0	16

[00228] The PEG is heated to 70° C and mixed until melted. The shellac powder is screened through a #40 mesh screen, and then added to the molten PEG. The combined ingredients are mixed until all powder is dispersed. The triethyl citrate is added next and the ingredients are mixed for one minute. PEO is added to the mixture and the ingredients are again mixed for 10 minutes. Croscarmellose sodium is then added followed by mixing for two additional minutes. Finally, dextromethorphan HBr is added and the ingredients are mixed for two more minutes.

[00229] The thermal cycle molding modules have the general configuration shown in Figure 3 and pages 27-51 of copending U.S. Application Serial No. 09/966,497, which depicts a thermal cycle molding module 200 comprising a rotor 202 around which a plurality of mold units 204 are disposed. The thermal cycle molding modules include reservoirs 206 (see Figure 4) for holding the core flowable material, the first shell portion flowable material, and the second shell portion flowable material. In addition, each thermal cycle molding module is provided with a temperature control system for rapidly heating and cooling the mold units. Figures 55 and 56 of pending U.S. Application Serial No. 09/966,497 depict the temperature control system 600.

[00230] The cores are made in a first thermal cycle molding module, which is linked via a transfer device to a second thermal cycle molding module. The first thermal cycle molding module has the specific configuration shown in Figure 26A of copending U.S. Application Serial No. 09/966,497. The first thermal cycle molding module comprises center mold assemblies 212 and upper mold assemblies 214 as shown in Figure 26C of copending

U.S. Application Serial No. 09/966,497, which mate to form mold cavities having a tablet shape. As rotor 202 rotates, the opposing center and upper mold assemblies close. Core flowable material, which is heated to a flowable state in reservoir 206, is injected into the resulting mold cavities. The temperature of the core flowable material is then decreased, hardening the core flowable material into tablet-shaped cores. The mold assemblies open and eject the cores, which are received by the first transfer device.

[00231] The transfer device has the structure shown as 300 in Figure 3 and described on pages 51-57 of copending U.S. Application Serial No. 09/966,414, the disclosure of which is incorporated by reference. It comprises a plurality of transfer units 304 attached in cantilever fashion to a belt 312 as shown in Figures 68 and 69. The transfer device rotates and operates in sync with the thermal cycle molding modules to which it is coupled. Transfer units 304 comprise retainers 330 for holding the cores as they travel around the transfer device.

[00232] The transfer device transfers the cores to the second thermal cycle molding module, which applies the shell to the cores. The second thermal cycle molding module is of the type shown in Figure 28A of copending U.S. Application Serial No. 09/966,497. The mold units 204 of the second thermal cycle molding module comprise upper mold assemblies 214, rotatable center mold assemblies 212 and lower mold assemblies 210 as shown in Figure 28C. Cores are continuously transferred to the mold assemblies, which then close over the cores.

[00233] Coating is performed in two steps, the first and second shell portions being applied separately as shown in the flow diagram of Figure 28B of copending U.S. Application Serial No. 09/966,497. In a first step, first shell portion flowable material, heated to a flowable state in reservoir 206, is injected into the mold cavities created by the closed

mold assemblies. The temperature of the first shell portion flowable material is then decreased, hardening it over half the core. The mold assemblies separate, the center mold assembly rotates, and then the mold assemblies again close. In a second step, second shell portion flowable material, heated to a flowable state in reservoir 206, is injected into the mold cavities. The temperature of the second shell portion flowable material is then decreased, hardening it over the other half of the core. The mold assemblies separate, and the finished dosage forms are ejected from the apparatus.

[00234] Although this invention has been illustrated by reference to specific embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made which clearly fall within the scope of this invention.

The invention claimed is:

1. A dosage form comprising :
 - (a) at least one active ingredient;
 - (a) a core; and
 - (b) a shell which resides upon at least a portion of the core, wherein the shell is substantially free of pores having a diameter of 0.5 to 5.0 microns; the shell comprises a first shell portion and a second shell portion which are compositionally different; and the dosage form provides a modified release profile of the active ingredient upon contacting of the dosage form with a liquid medium.
2. The dosage form of Claim 1, in which at least one of the first or second shell portions comprises means for modifying the release profile of an active ingredient contained either in (i) the core or (ii) the shell portion comprising the means for modifying the release profile upon contacting of the dosage form with a liquid medium.
3. The dosage form of Claim 1 in which at least one of the first or second shell portions comprises an active ingredient.
4. The dosage form of Claim 1, in which the first and second shell portions each comprise an active ingredient.
5. The dosage form of Claim 1, in which at least one of the first or second shell portions comprises an active ingredient which is immediately released therefrom upon contacting of the dosage form with a liquid medium.
6. The dosage form of Claim 1, in which at least one of the first or second shell portions provides modified release of at least one active ingredient contained therein.

7. The dosage form of Claim 1, in which at least one of the first or second shell portions comprises at least one active ingredient, and the release of the active ingredient contained in the shell portion is sustained, prolonged, extended, or retarded upon contacting of the dosage form with a liquid medium.

8. The dosage form of Claim 4, in which the first and second shell portions each provide different release profiles for the active ingredients contained therein upon contacting of the dosage form with a liquid medium.

9. The dosage form of Claim 1, in which at least one of the first or second shell portions provides modified release of at least one active ingredient contained in the underlying core or portion thereof.

10. The dosage form of Claim 1, in which the core comprises particles comprising the active material.

11. The dosage form of Claim 6, in which the particles comprise a coating capable of providing a modified release profile of the active ingredient in the particles upon contacting of the core with a liquid medium.

12. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and at least one active ingredient contained in the first or second core portion exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

13. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the first or second core portion comprises a material which provides a modification to the

release of an active ingredient contained therein upon contacting of the dosage form with a liquid medium.

14. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the first or second shell portion comprises a material which provides a modification to the release of an active ingredient contained in the underlying core portion upon contacting of the dosage form with a liquid medium.

15. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, at least one core portion comprises at least one active ingredient, and the release of the active ingredient contained in the core portion is delayed upon contacting of the dosage form with a liquid medium.

16. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, and at least one core portion comprises at least one active ingredient, and the release of the active ingredient contained in the core portion is sustained, prolonged, extended, or retarded upon contacting of the dosage form with a liquid medium.

17. The dosage form of Claim 1, in which at least one of the first or second core portions comprises an active ingredient which is immediately released therefrom upon breach of the surrounding shell portion and contacting of the core portion with a liquid medium.

18. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, each core portion comprises an active ingredient, and each of the active ingredients exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

19. The dosage form of Claim 18, in which the release profiles of the active ingredients in the first and second core portions are substantially similar.

20. The dosage form of Claim 18, in which the release profiles of the first and second core portions are substantially different.

21. The dosage form of Claim 1, in which the core comprises a first core portion and a second core portion, only one of the first or second core portions comprises an active ingredient, and the active ingredient exhibits a modified release profile upon contacting of the dosage form with a liquid medium.

22. The dosage form of Claim 1, in which the core is a bi-layer tablet.

23. The dosage form of Claim 1, in which at least one of the first or second core portions comprises particles comprising at least one active ingredient.

24. The dosage form of Claim 23, in which the particles comprise a coating capable of providing a modified release profile of the active ingredient in the particles upon contacting of the core with a liquid medium.

25. The dosage form of Claim 1, in which the core is substantially free of pores having a diameter of 0.5-5.0 microns.

26. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core comprising first and second core portions; and
- (c) a shell portion which surrounds at least one of the first or second core portions.

27. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core comprising first and second core portions; and
- (c) a shell portion which surrounds only the first core portion, wherein the second core portion is not enclosed by a shell portion, and the second core portion is exposed immediately to the liquid medium upon contact of the dosage form with a liquid medium.

28. A dosage form comprising:

- (a) at least one active ingredient;
- (b) a core comprising first and second core portions; and
- (c) a shell which resides upon at least a portion of the core, wherein the shell comprises first and second shell portions such that the first shell portion resides upon at least a portion of the first core portion and the second shell portion resides upon at least a portion of the second core portion, and at least one of the first or second core portions or first or second shell portions provides a modified release profile of an active ingredient upon contacting of the dosage form with a liquid medium.

29. The dosage form of Claim 28, in which the first core portion comprises a first active ingredient, and the second core portion does not comprise an active ingredient.

30. The dosage form of Claim 28, in which the first core portion comprises a first active ingredient, and the second core portion comprises a second active ingredient.

31. The dosage form of Claim 30, in which the first shell portion provides for modified release of the first active ingredient, and the second shell portion provides for modified release of the second active ingredient.

32. The dosage form of Claim 30, in which the first shell portion provides for immediate release of the first active ingredient, and the second shell portion provides for modified release of the second active ingredient.

33. The dosage form of Claim 28, in which the first core portion comprises a first active ingredient, the second core portion comprises a second active ingredient, the first shell portion comprises a third active ingredient, and the second shell portion comprises a fourth active ingredient.

34. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing an erosion controlled release profile of at least one active ingredient.

35. The dosage form of Claim 34, wherein the dosage form comprises means for providing an erosion controlled release profile of an active ingredient contained in the core.

36. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing a diffusion controlled release profile of at least one active ingredient.

37. The dosage form of Claim 36, wherein the dosage form comprises means for providing a diffusion controlled release profile of an active ingredient contained in the core.

38. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing an immediate release profile for an active ingredient contained in the shell.

39. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing a delayed release profile for an active ingredient contained in the core.

40. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing an immediate release profile of an active ingredient contained in the core upon a breach of the shell by the liquid medium.

41. The dosage form of Claim 28, in which at least one of the first or second core portions is substantially free of pores having a diameter of 0.5-5.0 microns.

42. The dosage form of Claim 28, in which at least one of the first or second shell portions is substantially free of pores having a diameter of 0.5-5.0 microns.

43. The dosage form of Claim 1 or Claim 28, wherein the dosage form comprises means for providing a pulsatile release profile of at least one active ingredient.

44. The dosage form of Claim 1 or Claim 28, wherein one or more shell portions prevent release therethrough of an active ingredient contained in the underlying core or core portion.

45. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions comprises a thermal-reversible carrier selected from the group consisting of polyethylene glycol, polyethylene oxide and combinations thereof.

46. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions comprises a release modifying excipient selected from the group consisting of shellac, hydroxypropylmethylcellulose, polyethylene oxide, ammonio methacrylate copolymer type B, and combinations thereof.

47. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions comprises a film-former selected from the group consisting of cellulose

acetate, ammonio methacrylate copolymer type B, shellac, hydroxypropylmethylcellulose, and combinations thereof.

48. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions comprises a swellable erodible hydrophilic material selected from the group consisting of selected from cross-linked polyvinyl pyrrolidone, cross-linked agar, cross-linked carboxymethylcellulose sodium, and combinations thereof.

49. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions further comprises a plasticizer.

50. The dosage form of Claim 1 or Claim 28, wherein at least one of the first or second shell portions comprises a pore former.

51. The dosage form of Claim 1 or Claim 28, further comprising an outer coating which covers at least a portion of the shell.

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FIG. 1

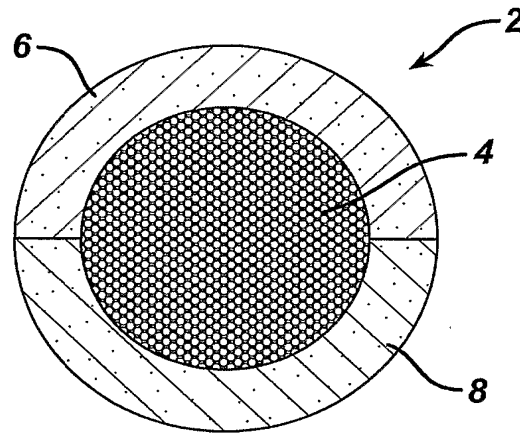
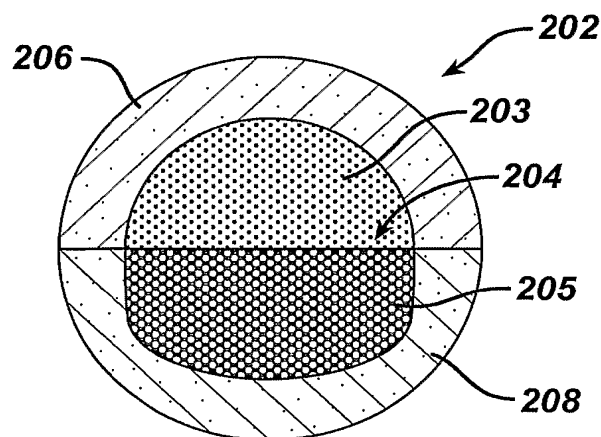
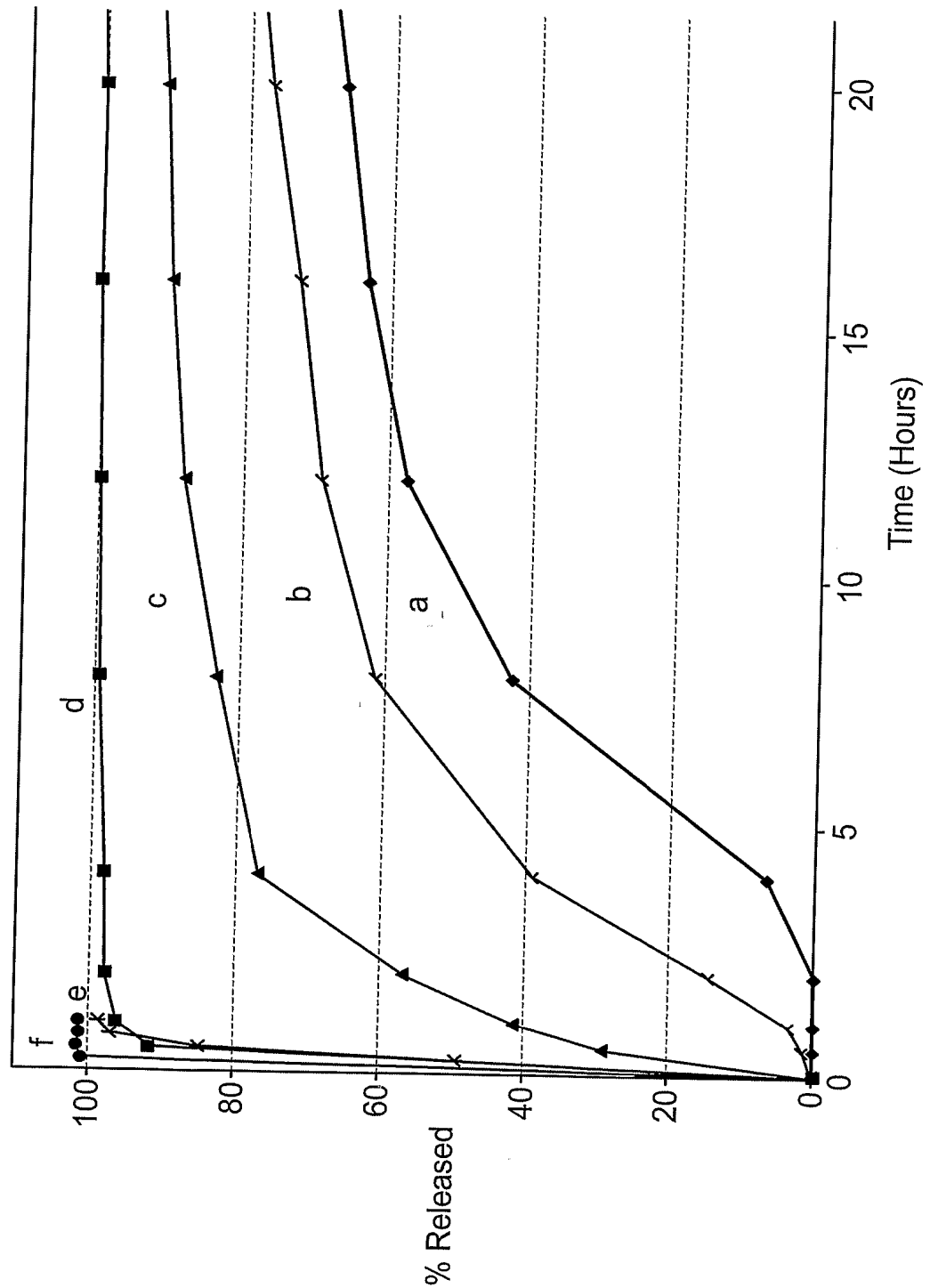


FIG. 2



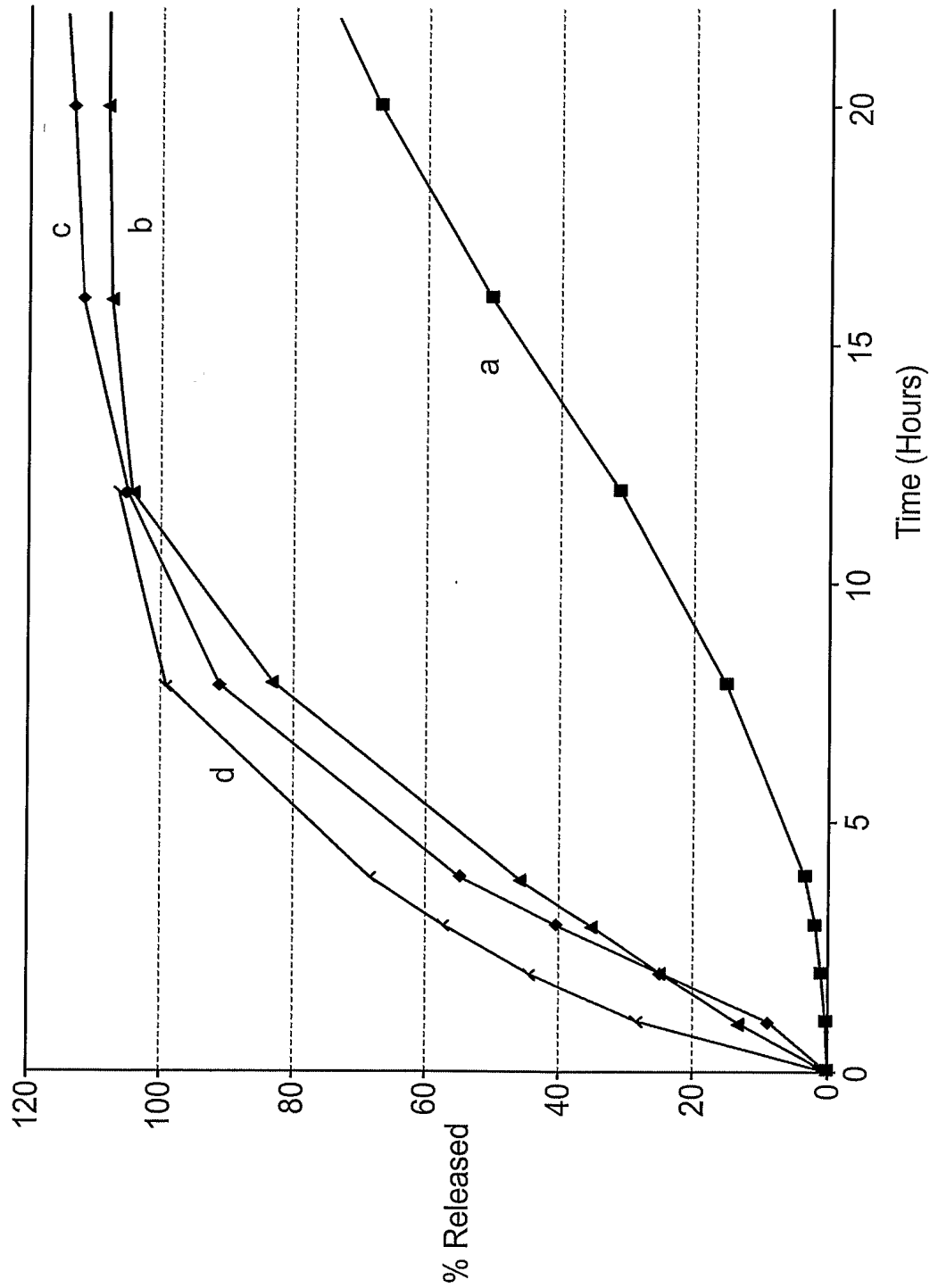
2/3

FIG. 3



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FIG. 4



INTERNATIONAL SEARCH REPORT

International () cation No
PCT/US 02/31024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 788 790 A (JAGOTEC AG) 13 August 1997 (1997-08-13) cited in the application figures; examples ---	1, 26-28
X	WO 94 06416 A (JAGOTEC AG ; CONTE UBALDO (IT); MAGGI LAURETTA (IT); MANNA ALDO (IT) 31 March 1994 (1994-03-31) cited in the application figure 2; examples 1-3, 5 ---	1
X	WO 99 51209 A (IMPAX PHARMACEUTICALS INC) 14 October 1999 (1999-10-14) cited in the application figure 2; example 2 ---	1
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

11 February 2003

Date of mailing of the international search report

26/02/2003

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/31024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 464 633 A (LA MANNA ALDO ET AL) 7 November 1995 (1995-11-07) cited in the application claim 15; figure 1 ----	1
X	DE 198 34 180 A (BENCKISER NV) 3 February 2000 (2000-02-03) figures ----	1,26,28
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X	EP 1 077 065 A (CHUGAI PHARMACEUTICAL CO LTD) 21 February 2001 (2001-02-21) figures 3-5 -----	1,26,28

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/31024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 2-25, 29-51 (not searched), 1, 26-28 (partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 2-25, 29-51 (not searched), 1, 26-28 (partially)

Claims 2-25 and 29-51 have been not searched and claims 1 and 26-28 have been searched partially for the following reasons:

Present independent claims 1, 26, 27 and 28 relate to an extremely large number of possible products ("dosage form", "active ingredient"). Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products claimed ("pharmaceutically active ingredient").

The further characterizing parameter "wherein the shell is substantially free of pores having a diameter of 0.5 to 5.0 microns" in claim 1 is considered to lead to a lack of clarity within the meaning of Article 6 PCT.

It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

In view of the large number and also the wording of the dependent claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search is impossible.

Consequently, the search has been carried out for those parts of the independent claims 1, 26, 27 and 28 which appear to be clear, supported and disclosed, namely those parts relating to the products prepared in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International cation No

PCT/US 02/31024

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